STIC Search Report
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STIC Database Tracking Number: 167745

TO: Ralph J Gitomer **Location: 3d65 / 3c18** **Art Unit: 1655** **Monday, October 24, 2005** **Case Serial Number: 10/749714**	**From: Noble Jarrell** **Location: Biotech-Chem Library** **Rem 1B71** **Phone: 272-2556** **Noble.jarrell@uspto.gov**

Search Notes

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     FILE 'HCAPLUS' ENTERED AT 10:15:40 ON 24 OCT 2005
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                /PN OR (US2003-749714# OR US2001-886143# OR US2000-215729#)/AP,
                PRN

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     FILE 'HCAPLUS' ENTERED AT 10:17:57 ON 24 OCT 2005
L2            TRA L1 1- RN :       10 TERMS

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L3           10 SEA ABB=ON  PLU=ON  L2

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L4            1 SEA ABB=ON  PLU=ON  (US2004248231 OR US6713276 OR US2002159991)
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                PRN

=> b hcap
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FILE LAST UPDATED: 23 Oct 2005  (20051023/ED)

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 This file contains CAS Registry Numbers for easy and accurate
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=> d all l1 tot

L1   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:10716  HCAPLUS
DN   136:81953
ED   Entered STN:  04 Jan 2002
TI   Non-amyloidogenic processing of β-amyloid precursor protein
     (βAPP) by β-secretase BACE2, use in suppression of
     β-amyloid production and screening of Alzheimer's disease drug
     candidates
IN   Cordell, Barbara; Schimmoller, Frauke; Liu, Yu-Wang; Quon, Diana Hom
PA   Scios Inc., USA
SO   PCT Int. Appl., 48 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C12P021-00
CC   7-2 (Enzymes)
     Section cross-reference(s): 9, 14
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FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2002000913	A2	20020103	WO 2001-US20465	20010627	<--
	WO 2002000913	C2	20021024			
	WO 2002000913	A3	20030313			
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
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	US 6713276	B2	20040330			
	CA 2413209	AA	20020103	CA 2001-2413209	20010627	<--
	EP 1315516	A2	20030604	EP 2001-948768	20010627	<--
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	JP 2004501652	T2	20040122	JP 2002-506227	20010627	<--
	US 2004248231	A1	20041209	US 2003-749714	20031231	<--
PRAI	US 2000-215729P	P	20000628	<--		
	US 2001-886143	A3	20010620	<--		
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2002000913	ICM	C12P021-00	
WO 2002000913	ECLA	C07K014/47A3; C12N009/64F	<--
US 2002159991	NCL	424/094.630	
	ECLA	C07K014/47A3; C12N009/64F	<--
JP 2004501652	FTERM	4B063/QA18; 4B063/QQ79; 4B063/QR16; 4B063/QR48; 4B063/QR56; 4B063/QS02; 4B063/QX07; 4B064/AG01; 4B064/CA21; 4B064/CB06; 4B064/CC03; 4B064/CD20; 4B064/DA01; 4B064/DA13; 4C084/AA19; 4C084/DC50; 4C084/NA14; 4C084/ZA02; 4C084/ZA16	<--
US 2004248231	NCL	435/023.000	
	ECLA	C07K014/47A3; C12N009/64F	<--

AB The present invention is based on the findings that BACE2, a homolog of β-secretase BACE, is able to stimulate processing of APP in a non-amyloidogenic pathway, thereby suppressing the level of Aβ. Accordingly, the present invention provides methods and means for the identification and use of modulators of this unique activity of BACE2 to suppress Aβ production The compds. identified using the methods and means provided herein may be used as potential candidates for the treatment of Alzheimer's disease and other neurol. diseases. Exptl. data disclosed herein confirm that BACE2 indeed possesses β-secretase activity when reconstituting β-secretase cleavage in a cellfree assay using wildtype (wt) or Swedish mutant forms of APP751 as a substrate. However, this activity is weaker than the β-secretase activity of BACE. The invention is further based on the unexpected finding that while BACE2 overexpression in HEK293 cells had a moderate effect on β-NTF formation, it strikingly suppressed Aβ production in either the presence or absence of addnl. exogenous copies of BACE. BACE2 also modulated Aβ levels in neuronal SKN cells and thus its effect was not restricted to nonneuronal HEK293 cells. The suppression of Aβ production by BACE2 did not appear to require its ability to cleave at the β-secretase site. A levels were similarly suppressed in cells carrying a C-terminal 100-amino acids fragment of amyloid precursor protein (APP) truncated to mimic β-secretase cleavage. It is suggested that BACE2 functions as a modulator of A production by promoting the alternative non-amyloidogenic APP processing pathway such as that mediated by α-secretase activity. Taken together, these data indicate that

the ability of BACE2 to suppress A production reflects enhanced α-secretase-like activity that is independent of prior β-secretase cleavage. This α-secretase-like activity of BACE2 promotes the non-amyloidogenic processing of APP or APP fragments and reduces the production of Aβ. In summary, results disclosed herein indicate that BACE2 possesses weaker β-secretase activity than BACE and competes with BACE in an allosteric manner. This competition is further enhanced when mutating the critical aspartate of BACE2 thereby eliminating its β-secretase activity. We also demonstrated that BACE2 interferes with Aβ production by an enzymic mechanism that depends on its proteolytic activity. BACE2 appears critically involved in APP processing towards the non-amyloidogenic pathway by promoting an α-secretase-like cleavage which results in reduced AP3 generation.

ST nonamyloidogenic APP processing secretase BACE2 drug screening Alzheimer disease

IT Nervous system
(central, reducing Aβ deposit in; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Alzheimer's disease
Drug screening
(non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Brain
(reducing Aβ deposit in; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(β-; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid precursor proteins
RL: ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(β-CTF of, formation by BACE2 of; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 148125-60-4, A4751 Amyloid protein precursor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cleavage by BACE2; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 158736-49-3, Aspartic protease BACE2
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); CAT (Catalyst use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 386303-49-7, 1: PN: WO0200913 SEQID: 1 unclaimed DNA 386303-51-1
386303-52-2
RL: PRP (Properties)
(unclaimed nucleotide sequence; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)
IT 386303-50-0
RL: PRP (Properties)
(unclaimed protein sequence; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)
IT 387398-33-6 387398-35-8
RL: PRP (Properties)
(unclaimed sequence; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)
IT 338454-52-7, γ-Secretase 338455-07-5, α-Secretase
RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL (Biological study); USES (Uses)
(use in inhibiting Aβ formation; non-amyloidogenic processing of β-amyloid precursor protein (βAPP) by β-secretase BACE2, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

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* *
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RN 387398-35-8 REGISTRY
ED Entered STN: 28 Jan 2002
CN L-Serine, L-cysteinyl-L-glutaminyl-L-arginyl-L-arginyl-L-prolyl-L-arginyl-L-α-aspartyl-L-prolyl-L-α-glutamyl-L-valyl-L-valyl-L-asparaginyl-L-α-aspartyl-L-α-glutamyl-L-seryl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 6: PN: WO0200913 SEQID: 6 unclaimed sequence
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C74 H123 N27 O29 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.

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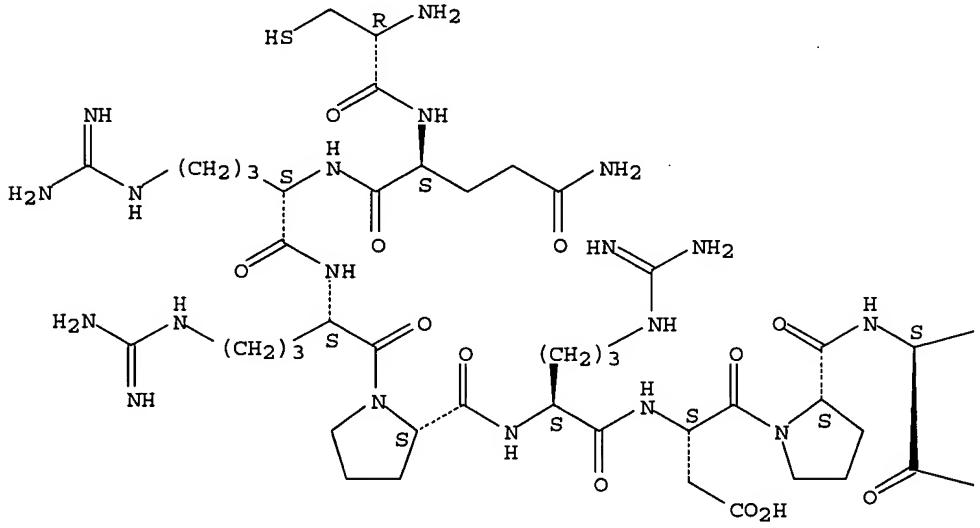

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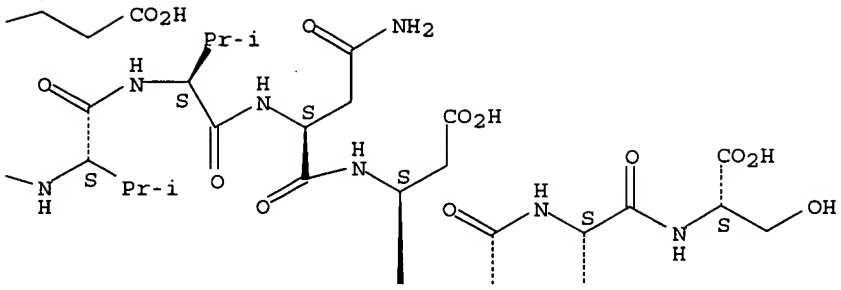

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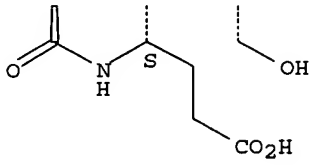

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RN 387398-33-6 REGISTRY
ED Entered STN: 28 Jan 2002
CN L-Leucine, L-cysteinyl-L-leucyl-L-arginyl-L-glutaminyl-L-glutaminyl-L-histidyl-L-α-aspartyl-L-α-aspartyl-L-phenylalanyl-L-alanyl-L-α-aspartyl-L-α-aspartyl-L-isoleucyl-L-seryl-L-leucyl- (9CI) (CA INDEX NAME)
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FS PROTEIN SEQUENCE; STEREOSEARCH
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Absolute stereochemistry.

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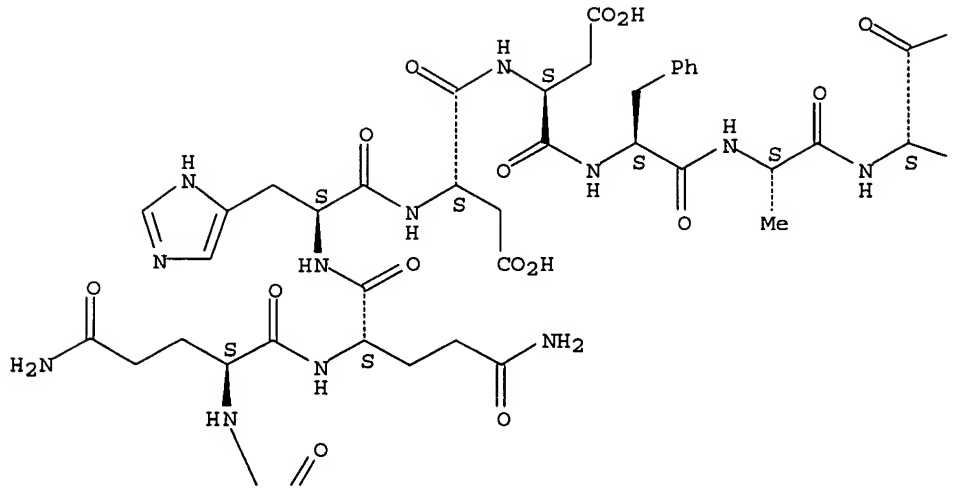

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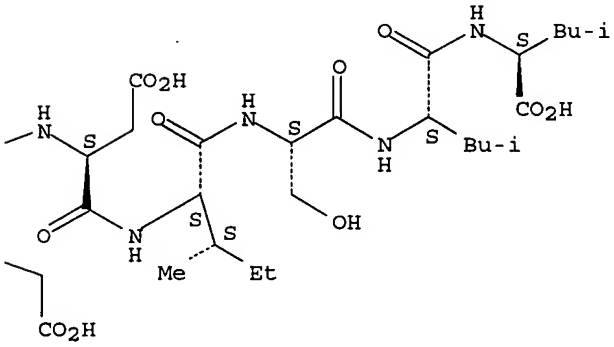

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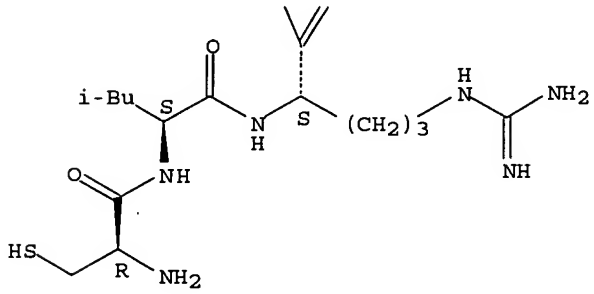

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L3 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **386303-52-2** REGISTRY
ED Entered STN: 24 Jan 2002
CN DNA, d(C-A-A-A-G-T-T-A-C-T-G-C-T-T-C-C-A-G-T-G-G-C-A-A-C-G-A-G-A-A-T-C-T-G-T-A-G-C) (9CI) (CA INDEX NAME)
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FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **386303-51-1** REGISTRY
ED Entered STN: 24 Jan 2002
CN DNA, d(G-C-T-A-C-A-G-A-T-T-C-T-C-G-T-T-G-C-C-A-C-T-G-G-A-A-G-C-A-G-T-A-A-C-T-T-T-G) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO0200913 SEQID: 3 unclaimed DNA
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **386303-50-0** REGISTRY
ED Entered STN: 24 Jan 2002
CN 2: PN: WO0200913 SEQID: 2 unclaimed protein (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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L3 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **386303-49-7** REGISTRY
ED Entered STN: 24 Jan 2002
CN 1: PN: WO0200913 SEQID: 1 unclaimed DNA (9CI) (CA INDEX NAME)
FS NUCLEIC ACID SEQUENCE
MF Unspecified

CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **338455-07-5** REGISTRY
ED Entered STN: 25 May 2001
CN α-Secretase (9CI) (CA INDEX NAME)
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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L3 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **338454-52-7** REGISTRY
ED Entered STN: 25 May 2001
CN γ-Secretase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ε-Secretase
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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715 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN **158736-49-3** REGISTRY
ED Entered STN: 04 Nov 1994
CN β-Secretase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN β Protein amyloidogenase
CN β-Amyloid converting enzyme
CN β-Amyloid protein precursor secretase
CN β-Site APP-cleaving enzyme
CN β-site APP-cleaving enzyme 1
CN Amyloid precursor protein secretase
CN APP secretase
CN Aspartic protease BACE
CN Aspartic protease BACE1
CN Aspartic proteinase BACE1
CN D-Aspartyl-β-amyloid secretase
CN Memapsin 2
CN Protease Asp2
CN Proteinase Asp2
CN Proteinase BACE1
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CIN, PROMT, TOXCENTER, USPAT2, USPATFULL

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             974 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3   ANSWER 10 OF 10  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   148125-60-4  REGISTRY
ED   Entered STN:  16 Jun 1993
CN   Proteinase inhibitor, protease-nexin II (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   A4751 amyloid protein precursor
CN   Amyloid A4751 glycoproteins
CN   Amyloid A4751 proteins
CN   Glycoproteins, amyloid A4751
CN   Glycoproteins, amyloid A4751
CN   Plasminogen activator inhibitor PN 2
CN   Protease-nexin 2
CN   Protease-nexin II
CN   Proteins, ABPP 751
CN   Proteins, amyloid A4751
CN   Proteins, amyloid precursor protein 751
CN   Proteins, APP751
CN   Proteins, BPP751
CN   Proteins, protease-nexins, II
CN   Proteins, proteinase-nexins II
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOSIS, CA, CAPLUS, PROMT, TOXCENTER, USPAT2, USPATFULL

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             131 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> b wpix;d all l4 tot
FILE 'WPIX' ENTERED AT 10:19:08 ON 24 OCT 2005
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FILE LAST UPDATED:          19 OCT 2005      <20051019/UP>
MOST RECENT DERWENT UPDATE:     200567        <200567/DW>
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L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2002-139929 [18] WPIX
DNC C2002-043150
TI Modulating enzymatic production of beta amyloid peptide from its precursor protein (APP) for treating Alzheimer's disease, comprises contacting APP with a beta site APP-cleaving enzyme 2 polypeptide, its agonist or antagonist.
DC B04 D16
IN CORDELL, B; LIU, Y; QUON, D H; SCHIMMOLLER, F; SCHIMMOELLER, F
PA (SCIO-N) SCIOS INC; (CORD-I) CORDELL B; (LIUY-I) LIU Y; (QUON-I) QUON D H; (SCHI-I) SCHIMMOLLER F
CYC 95
PI WO 2002000913 A2 20020103 (200218)* EN 48 C12P021-00
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AU 2001070204 A 20020108 (200235) C12P021-00
US 2002159991 A1 20021031 (200274) A61K038-48 <--
EP 1315516 A2 20030604 (200337) EN A61K038-48
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004501652 W 20040122 (200411) 144 C12P021-06
US 6713276 B2 20040330 (200423) C12Q001-37 <--
US 2004248231 A1 20041209 (200481) C12Q001-37 <--
ADT WO 2002000913 A2 WO 2001-US20465 20010627; AU 2001070204 A AU 2001-70204 20010627; US 2002159991 A1 **Provisional US 2000-215729P 20000628, US 2001-886143 20010620**; EP 1315516 A2 EP 2001-948768 20010627, WO 2001-US20465 20010627; JP 2004501652 W WO 2001-US20465 20010627, JP 2002-506227 20010627; US 6713276 B2 **Provisional US 2000-215729P 20000628, US 2001-886143 20010620**; US 2004248231 A1 **Provisional US 2000-215729P 20000628, Div ex US 2001-886143 20010620, US 2003-749714 20031231**
FDT AU 2001070204 A Based on WO 2002000913; EP 1315516 A2 Based on WO 2002000913; JP 2004501652 W Based on WO 2002000913; US 2004248231 A1 Div ex US 6713276
PRAI **US 2000-215729P 20000628; US 2001-886143 20010620; US 2003-749714 20031231**
IC ICM A61K038-48; C12P021-00; C12P021-06; C12Q001-37
ICS A61K038-00; A61K045-00; A61P025-00; A61P025-28; C12N009-99; G01N033-50
AB WO 200200913 A UPAB: 20020319
NOVELTY - Modulating (M1) the enzymatic production of beta -amyloid peptide (A beta) from beta -amyloid precursor protein (APP) or its fragment, involves contacting the APP or its fragment with a beta -site APP-cleaving enzyme (BACE)-2 polypeptide, its agonist or antagonist.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) inhibiting (M2) the release of a full-length A beta polypeptide from APP or its fragment, by cleaving APP or its fragment by a BACE2 polypeptide or its agonist at a site interfering with beta -secretase processing of the APP or its fragment;

(2) identifying (M3) a modulator of the enzymatic production of A beta from APP or its fragment, by contacting APP or its fragment and BACE2 with a candidate compound (CC) and monitoring the effect of CC on the production of A beta ; and

(3) a modulator (I) of the enzymatic production of A beta from APP or its fragment, identified by (M3).

ACTIVITY - Neuroprotective; nootropic.

MECHANISM OF ACTION - Enzymatic production inhibitor; release of A beta inhibitor; BACE2 agonist (claimed). Variable amounts of BACE2 or BACE expression plasmids were co-transfected with a constant amount of DNA encoding APP751sw (Swedish double mutant) substrate cDNA. Cell supernatants were collected 48 hours or 72 hours post-transfection and analyzed for alpha -NTF (undefined), -NTF, total A and A 42. Expression of APP751sw alone led to a significant increase in -NTF, alpha -NTF, total and A 42 compared to mock-transfected cells. This suggested that endogenous secretases were not limiting for -NTF or A formation under these conditions. When BACE was expressed in addition to APP751sw, -NTF levels were further increased, and alpha -NTF levels were proportionally reduced. Under these conditions, A production was not significantly stimulated. When co-transfecting BACE2 with APP751sw, the effect on -NTF levels was very similar to that of BACE suggesting that BACE had some secretase activity in vivo. In fact, the levels of alpha -NTF and -NTF generated by BACE2 and BACE were inversely proportional to each other and added upto basically the same total optical density (OD) values as in cells transfected with APP751sw alone (total OD approximately 2.59 for APP751sw alone, approximately 2.5 with BACE2, and approximately 2.3 with BACE). The combined values of alpha -NTF and -NTF for BACE was slightly lower since the -NTF assay had reached saturation. The different ratios of alpha -NTF and -NTF values under the different transfection conditions were consistent with the competition of secretase and secretase for the same substrate. The slightly higher levels of -NTF in conditioned medium from BACE2 versus BACE transfected cells reflects in part the fact that BACE2 is the weaker secretase. In contrast to BACE, BACE2 expression resulted in the striking reduction of total A and A 42 to levels found in mock-transfected cells. Thus, BACE2 suppressed A production without significantly affecting the formation of either alpha -NTF and -NTF.

USE - (I) and BACE2 are useful for reducing the amount of beta -amyloid deposits in the central nervous system (CNS) (e.g. brain) of a mammal, by the administration of BACE2 or its agonist to the mammal, e.g. a human. BACE2 and (I) are useful for the treatment or the prevention of Alzheimer's disease (AD), an AD-type pathology or cerebral amyloid angiopathy in a mammalian patient e.g. human, at a risk of developing AD, AD-type pathology or cerebral amyloid angiopathy (claimed).

Dwg.0/8

FS CPI
FA AB; DCN
MC CPI: B04-L01; B04-M01; B04-N02; B11-C08E3; B12-K04E; B14-J01A4; B14-L01; B14-L06; B14-N16; D05-C03; D05-C11; D05-H09

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=> d his

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L4            1 L1

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L6          151 (BSECRETASE? OR B(W)SECRETAS?)/CNS
L7          167 L5-6
L8            6 (MEMAPSIN2 OR MEMAPSIN (W)2)/CNS
L9          171 L7,L8

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L10        1030 L9
L11          58 MEMAPSIN2 OR MEMAPSIN(W)2
L12         937 BSECRETASE? OR B(W)SECRETAS?
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                E ALZHEIMER/CT
                E E9+ALL
L14             QUE "ALZHEIMER'S DISEASE"+OLD,NT/CT
                E E26+ALL
L15       79174 AGING, ANIMAL+OLD,NT/CT
                E AMYLOID PRECURSOR PROTEINS/CT
                E E3+ALL
L16        4880 AMYLOID PRECURSOR PROTEINS+OLD,NT/CT
                E AMYLOIDOSIS/CT
                E E3+ALL
L17        3539 AMYLOIDOSIS+OLD,NT/CT
                E "ANTI-ALZHEIMER'S AGENTS"/CT
                E E3+ALL
L18        6449 "ANTI-ALZHEIMER'S AGENTS"/CT
                E COGNITION ENHANCERS/CT
                E E3+ALL
L19        3595 COGNITION ENHANCERS+OLD/CT
                E AMYLOID/CT
                E E3+ALL
L20       93386 AMYLOID+OLD,NT/CT
                E NEUROFIBRILLARY TANGLE/CT
                E E3+ALL
L21        1268 NEUROFIBRILLARY TANGLE+OLD/CT
                E PRESENILINS/CT
                E E3+ALL
L22        1643 PRESENILINS/CT
                E TAU FACTOR/CT
                E E3+ALL
L23        3324 TAU FACTOR+OLD/CT
                E B-SECRETASE/CT
                E E3+ALL
L24         974 B-SECRETASE/CT
L25        1609 L10,L11,L12,L13,L24 AND L14-23
                E CORDELL B/AU
L26         111 E3-6
                E SCHIMMOLLER F/AU
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L29         1145 E3
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L30            9 E4
                 E LIU YUW/AU
L31           11 E4
                 E QUON D/AU
L32           72 E3-5,E9-11
L33          221 SCIOS/CS,PA
L34           21 L25 AND L26-33
L35        35605 DRUG SCREENING+OLD/CT
L36         1588 L25 NOT L34
L37           99 L36 AND L35
L38              QUE PY<=2000 OR AY<=2000 OR PRY<=2000 OR PD<20000628 OR AD<=200
L39           50 L37 AND L38
L40           50 L39 AND (BIOL+NT OR ANST+NT)/RL
                 SEL AN 21 23 26-28 37 38 43 44  L40
L41            9 E1-18 AND L40
                 SEL AN 2 7-8 10 11 16 L40
L42            6 E19-30 AND L40
L43           15 L41,L42

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FILE LAST UPDATED: 23 Oct 2005  (20051023/ED)

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=> d all l34 tot

L34  ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:865010  HCAPLUS
DN   138:361960
ED   Entered STN:  14 Nov 2002
TI   Amyloid forming proteases: therapeutic targets for Alzheimer's disease
AU   Schimmoller, Frauke; Higaki, Jeffrey N.; Cordell,
     Barbara
CS   Scios Inc., Sunnyvale, CA, 94085, USA
SO   Current Pharmaceutical Design (2002), 8(28), 2521-2531
     CODEN: CPDEFP; ISSN: 1381-6128
PB   Bentham Science Publishers
DT   Journal; General Review
LA   English
CC   1-0 (Pharmacology)
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AB A review. Alzheimer's disease is an age-related neurodegenerative disease which causes global loss of cognitive function. Drug treatment for Alzheimer's disease has been limited to agents that ameliorate behavioral symptoms but these agents are without effect on disease progression. Rational drug design for the treatment of Alzheimer's disease now seems possible. As a result of major advances in medical research in this area, knowledge of the etiol. of Alzheimer's disease is rapidly being understood. This information has uncovered relevant and novel targets for treatment. At the center of the etiol. progression of this disease is β-amyloid. A substantial body of evidence strongly suggests that this small protein is critical to the development of Alzheimer's disease. The β-amyloid protein is generated by two different proteolytic cleavages. Recently, the proteases responsible for producing the β-amyloid protein have been identified. The proteases represent viable targets for therapeutic intervention against Alzheimer's disease. In this review, we describe the biol. characteristics of the β-amyloid-forming proteases in the context of pharmaceutical development.

ST review amyloid protease drug target Alzheimer disease

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BACE; amyloid forming proteases as drug targets for Alzheimer's disease)

IT **Alzheimer's disease**
Anti-Alzheimer's agents
(amyloid forming proteases as drug targets for Alzheimer's disease)

IT Nervous system, disease
(degeneration; amyloid forming proteases as drug targets for Alzheimer's disease)

IT **Amyloid**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-; amyloid forming proteases as drug targets for Alzheimer's disease)

IT **158736-49-3, β -Secretase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(amyloid forming proteases as drug targets for Alzheimer's disease)

RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Acquati, F; FEBS Lett 2000, V468, P59 HCAPLUS
(2) Beeson, J; J Comp Neurol 1994, V342, P69 HCAPLUS
(3) Bennett, B; J Biol Chem 2000, V275, P20647 HCAPLUS
(4) Bennett, B; J Biol Chem 2000, V275, P37712 HCAPLUS
(5) Berechid, B; Current Biology 1999, V9, P1493 HCAPLUS
(6) Berezovska, O; J Neurochem 2000, V75, P583 HCAPLUS
(7) Borschelt, D; Neuron 1996, V17, P1005
(8) Bretscher, M; Science 1993, V261, P1280 HCAPLUS
(9) Cai, X; Science 1993, V259, P514 HCAPLUS
(10) Capell, A; J Biol Chem 2000, V275, P30849 HCAPLUS
(11) Capell, A; Nature Cell Biol 2000, V2, P205 HCAPLUS
(12) Citron, M; Nature 1992, V360, P672 HCAPLUS
(13) Citron, M; Nature Med 1997, V3, P67 HCAPLUS
(14) Citron, M; Proc Natl Acad Sci USA 1996, V93, P13170 HCAPLUS
(15) Cook, D; Nature Med 1997, V3, P1021 HCAPLUS
(16) Cordell, B; Annu Rev Pharmacol Toxicol 1994, V34, P69 HCAPLUS
(17) Creemers, J; J Biol Chem 2000
(18) Cummings, B; Neurobiol Learn Mem 1996, V66, P11 HCAPLUS
(19) De Strooper, B; J Cell Sci 2000, V113, P1857 HCAPLUS
(20) De Strooper, B; Nature 1998, V391, P387 HCAPLUS
(21) De Strooper, B; Nature 1999, V398, P518 HCAPLUS
(22) Dovey, H; J Neurochem 2001, V76, P173 HCAPLUS
(23) Duff, K; Nature 1996, V383, P710 HCAPLUS
(24) Duyckaerts, C; J Neurol 1990, V97, P295 MEDLINE
(25) Elser, W; Nature Cell Biol 2000, V2, P428
(26) Ermolieff, J; Biochem 2000, V39, P12450 HCAPLUS
(27) Farzan, M; Proc Natl Acad Sci USA 2000, V97, P9712 HCAPLUS
(28) Figueiredo-Pereira, M; J Neurochem 1999, V72, P1417 HCAPLUS

(29) Glenner, G; Biochim Biophys Res Commun 1984, V120, P885 HCAPLUS
(30) Gosh, A; J Am Chem Soc 2000, V122, P3522
(31) Haniu, M; J Biol Chem 2000, V275, P21099 HCAPLUS
(32) Hartmann, T; Nature Med 1997, V3, P1016 HCAPLUS
(33) Herreman, A; Nature Cell Biol 2000, V2, P461 HCAPLUS
(34) Higaki, J; J Med Chem 1999, V42, P3889 HCAPLUS
(35) Higaki, J; Neuron 1995, V14, P651 HCAPLUS
(36) Hong, L; Science 2000, V290, P150 HCAPLUS
(37) Huse, J; J Biol Chem 2000, V275, P33729 HCAPLUS
(38) Hussain, I; Mol Cell Neurosci 1999, V14, P419 HCAPLUS
(39) Hussain, I; Mol Cell Neurosci 2000, V16, P609 HCAPLUS
(40) Janus, C; Biochim Biophy Acta 2000, V1502, P63 HCAPLUS
(41) Jarrett, J; Cell 1993, V73, P1055 HCAPLUS
(42) Katayama, T; Nature Cell Biol 1999, V1, P479 HCAPLUS
(43) Kimberly, W; J Biol Chem 2000, V275, P3173 HCAPLUS
(44) Klafki, H; J Biol Chem 1996, V271, P28655 HCAPLUS
(45) Kulic, L; Proc Natl Acad Sci USA 2000, V97, P5913 HCAPLUS
(46) Li, Y; Nature 2000, V405, P689 HCAPLUS
(47) Li, Y; Proc Natl Acad Sci USA 2000, V97, P6138 HCAPLUS
(48) Lichtenthaler, S; Biochemistry 1997, V36, P15396 HCAPLUS
(49) Lichtenthaler, S; Proc Natl Acad Sci USA 1999, V96, P3053 HCAPLUS
(50) Lin, X; Proc Natl Acad Sci USA 2000, V97, P1456 HCAPLUS
(51) Maruyama, K; Biochem Biophys Res Comm 1996, V227, P730 HCAPLUS
(52) Masters, C; Proc Natl Acad Sci USA 1985, V82, P4245 HCAPLUS
(53) McLendon, C; FASEB J 2000, V14, P2383 HCAPLUS
(54) Molloy, S; Trends Cell Biol 1999, V9, P28 HCAPLUS
(55) Moore, C; J Med Chem 2000, V43, P3434 HCAPLUS
(56) Mullan, M; Nat Genet 1992, V1, P345 HCAPLUS
(57) Naruse, S; Neuron 1998, V21, P1213 HCAPLUS
(58) Nishimura, M; Nature Medicine 1999, V5, P164 HCAPLUS
(59) Niwa, M; Cell 1999, V99, P691 HCAPLUS
(60) Palacino, J; J Biol Chem 2000, V275, P215 HCAPLUS
(61) Saunders, A; Neuropath & Exptl Neurol 2000, V59, P751 HCAPLUS
(62) Saunders, A; Science 1999, V286, P1255
(63) Schellenberg, G; Proc Natl Acad Sci USA 1995, V92, P8552 HCAPLUS
(64) Schroeter, E; Nature 1998, V393, P382 HCAPLUS
(65) Schuener, D; Nature Med 1996, V2, P864
(66) Seiffert, D; J Biol Chem 2000, V275, P34086 HCAPLUS
(67) Selkoe, D; Nature 1999, V399, PA23 HCAPLUS
(68) Shearman, M; Biochemistry 2000, V39, P8698 HCAPLUS
(69) Sherrington, R; Nature 1995, V375, P754 HCAPLUS
(70) Shi, X; J Biol Chem 2000
(71) Sinha, S; J Nature 1999, V402, P537 HCAPLUS
(72) Song, W; Proc Natl Acad Sci 1999, V96, P6959 HCAPLUS
(73) Steiner, H; J Biol Chem 1999, V274, P28669 HCAPLUS
(74) Steiner, H; Nature Cell Biol 2000, V2, P848 HCAPLUS
(75) Struble, R; Brain Res 1985, V361, P267 MEDLINE
(76) Struhl, G; Nature 1999, V398, P522 HCAPLUS
(77) Sudoh, S; J Neurochem 1998, V71, P1535 HCAPLUS
(78) Tang, J; J Cell Biochem 1987, V33, P53 HCAPLUS
(79) Tischer, E; J Biol Chem 1996, V271, P21914 HCAPLUS
(80) Vassar, R; Neuron 2000, V27, P419 HCAPLUS
(81) Vassar, R; Science 1999, V286, P735 HCAPLUS
(82) Verdile, G; J Biol Chem 2000, P20794 HCAPLUS
(83) Walker, L; Neurobiol Aging 1988, V9, P657 MEDLINE
(84) Weidemann, A; Nature Med 1997, V3, P328 HCAPLUS
(85) Wild-Bode, C; J Biol Chem 1997, V272, P16085 HCAPLUS
(86) Wolfe, M; Biochemistry 1999, V38, P4720 HCAPLUS
(87) Wolfe, M; J Med Chem 1998, V41, P6 HCAPLUS
(88) Wolfe, M; Nature 1999, V398, P513 HCAPLUS
(89) Xia, W; Proc Natl Acad Sci USA 1997, V94, P8208 HCAPLUS
(90) Yamazaki, T; Biochemistry 1997, V36, P8377 HCAPLUS
(91) Yan, R; Nature 1999, V402, P533 HCAPLUS
(92) Ye, Y; Nature 1999, V398, P525 HCAPLUS
(93) Yu, G; J Biol Chem 1998, V273, P16470 HCAPLUS
(94) Yu, G; J Biol Chem 2000, V275, P27348 HCAPLUS

(95) Yu, G; Nature 2000, V407, P48 HCAPLUS

L34 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:10716 HCAPLUS
DN 136:81953
ED Entered STN: 04 Jan 2002
TI Non-amyloidogenic processing of β-amyloid precursor protein (. **beta.APP**) by β **-secretase** **BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates
IN **Cordell, Barbara; Schimmoller, Frauke; Liu, Yu-Wang; Quon, Diana Hom**
PA **Scios** Inc., USA
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12P021-00
CC 7-2 (Enzymes)
Section cross-reference(s): 9, 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002000913	A2	20020103	WO 2001-US20465	20010627
	WO 2002000913	C2	20021024		
	WO 2002000913	A3	20030313		
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	US 6713276	B2	20040330		
	CA 2413209	AA	20020103	CA 2001-2413209	20010627
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PRAI	US 2000-215729P	P	20000628		
	US 2001-886143	A3	20010620		
	WO 2001-US20465	W	20010627		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002000913	ICM	C12P021-00
WO 2002000913	ECLA	C07K014/47A3; C12N009/64F
US 2002159991	NCL	424/094.630
	ECLA	C07K014/47A3; C12N009/64F
JP 2004501652	FTERM	4B063/QA18; 4B063/QQ79; 4B063/QR16; 4B063/QR48; 4B063/QR56; 4B063/QS02; 4B063/QX07; 4B064/AG01; 4B064/CA21; 4B064/CB06; 4B064/CC03; 4B064/CD20; 4B064/DA01; 4B064/DA13; 4C084/AA19; 4C084/DC50; 4C084/NA14; 4C084/ZA02; 4C084/ZA16
US 2004248231	NCL	435/023.000
	ECLA	C07K014/47A3; C12N009/64F

AB The present invention is based on the findings that **BACE2**, a homolog of β **-secretase** BACE, is able to stimulate processing of APP in a non-amyloidogenic pathway, thereby suppressing the level of Aβ. Accordingly, the present invention provides methods and means for the identification and use of modulators of this unique activity

of **BACE2** to suppress Aβ production The compds. identified using the methods and means provided herein may be used as potential candidates for the treatment of Alzheimer's disease and other neurol. diseases. Exptl. data disclosed herein confirm that **BACE2** indeed possesses β -**secretase** activity when reconstituting β -**secretase** cleavage in a cellfree assay using wildtype (wt) or Swedish mutant forms of APP751 as a substrate. However, this activity is weaker than the β -**secretase** activity of BACE. The invention is further based on the unexpected finding that while **BACE2** overexpression in HEK293 cells had a moderate effect on β-NTF formation, it strikingly suppressed Aβ production in either the presence or absence of addnl. exogenous copies of BACE. **BACE2** also modulated Aβ levels in neuronal SKN cells and thus its effect was not restricted to nonneuronal HEK293 cells. The suppression of Aβ production by **BACE2** did not appear to require its ability to cleave at the . **beta.-secretase** site. A levels were similarly suppressed in cells carrying a C-terminal 100-amino acids fragment of amyloid precursor protein (APP) truncated to mimic β -**secretase** cleavage. It is suggested that **BACE2** functions as a modulator of A production by promoting the alternative non-amyloidogenic APP processing pathway such as that mediated by α-secretase activity. Taken together, these data indicate that the ability of **BACE2** to suppress A production reflects enhanced α-secretase-like activity that is independent of prior **.beta .-secretase** cleavage. This α-secretase-like activity of **BACE2** promotes the non-amyloidogenic processing of APP or APP fragments and reduces the production of Aβ. In summary, results disclosed herein indicate that **BACE2** possesses weaker . **beta.-secretase** activity than BACE and competes with BACE in an allosteric manner. This competition is further enhanced when mutating the critical aspartate of **BACE2** thereby eliminating its . **beta.-secretase** activity. We also demonstrated that **BACE2** interferes with Aβ production by an enzymic mechanism that depends on its proteolytic activity. **BACE2** appears critically involved in APP processing towards the non-amyloidogenic pathway by promoting an α-secretase-like cleavage which results in reduced AP3 generation.

ST nonamyloidogenic APP processing secretase **BACE2** drug screening Alzheimer disease

IT Nervous system
(central, reducing Aβ deposit in; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT **Alzheimer's disease**
Drug screening
(non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT **Amyloid precursor proteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT Brain
(reducing Aβ deposit in; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT **Amyloid**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study,

unclassified); BIOL (Biological study)
(β-; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT **Amyloid precursor proteins**
RL: ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(β-CTF of, formation by **BACE2** of; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 148125-60-4, A4751 Amyloid protein precursor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cleavage by **BACE2**; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT **158736-49-3**, Aspartic protease **BACE2**
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); CAT (Catalyst use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 386303-49-7, 1: PN: WO0200913 SEQID: 1 unclaimed DNA 386303-51-1 386303-52-2
RL: PRP (Properties)
(unclaimed nucleotide sequence; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 386303-50-0
RL: PRP (Properties)
(unclaimed protein sequence; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 387398-33-6 387398-35-8
RL: PRP (Properties)
(unclaimed sequence; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

IT 338454-52-7, γ-Secretase 338455-07-5, α-Secretase
RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL (Biological study); USES (Uses)
(use in inhibiting Aβ formation; non-amyloidogenic processing of β-amyloid precursor protein (β **APP**) by β -**secretase BACE2**, use in suppression of β-amyloid production and screening of Alzheimer's disease drug candidates)

L34 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:914735 HCAPLUS
DN 136:165334
ED Entered STN: 19 Dec 2001
TI Specific spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques

AU Koistinaho, Milla; Ort, Michael; Cimadevilla, Jose M.; Vondrous, Roman; **Cordell, Barbara**; Koistinaho, Jari; Bures, Jan; Higgins, Linda S.

CS Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, 14220/4, Czech Rep.

SO Proceedings of the National Academy of Sciences of the United States of America (2001), 98(25), 14675-14680
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)

AB Memory impairment progressing to dementia is the main clin. symptom of Alzheimer's disease (AD). AD is characterized histol. by the presence of β-amyloid (Aβ) plaques and neurofibrillary tangles in specific brain regions. Although Aβ derived from the Aβ precursor protein (β -**APP**) is believed to play a central etiol. role in AD, it is not clear whether soluble and/or fibrillar forms are responsible for the memory deficit. We have generated and previously described mice expressing human wild-type β -**APP751** isoform in neurons. These transgenic mice recapitulate early histopathol. features of AD and form Aβ deposits but no plaques. Here we describe a specific and progressive learning and memory impairment in these animals. In the Morris water maze, a spatial memory task sensitive to hippocampal damage, one pedigree already showed significant differences in acquisition in 3-mo-old mice that increased in severity with age and were expressed clearly in 6-mo- and 2-yr-old animals. The second transgenic pedigree displayed a milder impairment with a later age of onset. Performance deficits significantly decreased during the 6 days of training in young but not in aged transgenic animals. Both pedigrees of the transgenic mice differed from wild-type mice by less expressed increase of escape latencies after the platform position had been changed in the reversal experiment and by failure to prefer the goal quadrant in probe trials. Both pedigrees performed at wild-type level in a number of other tests (open field exploration and passive and active place avoidance). The results suggest that plaque formation is not a necessary condition for the neuronal β -**APP751** transgene-induced memory impairment, which may be caused by β -**APP** overexpression, isoform misexpression, or elevated soluble Aβ.

ST beta amyloid precursor protein spatial learning deficit transgenic mouse

IT Mental disorder
(memory retention defect; spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)

IT Memory, biological
(retention defect; spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)

IT **Aging, animal**
Alzheimer's disease
Disease models
Human
Mus
(spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)

IT **Amyloid precursor proteins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)

IT Learning
(spatial, disorder; spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)

IT Gene, animal

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(β -APP751; spatial learning deficits become severe with age in β-amyloid precursor protein transgenic mice that harbor diffuse β-amyloid deposits but do not form plaques)
RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Alkadhi, K; J Neurosci 2001, V21, P3515 HCAPLUS
(2) Arendash, G; Brain Res 2001, V891, P42 HCAPLUS
(3) Burger, P; Am J Pathol 1973, V73, P457 MEDLINE
(4) Campbell, A; Med Hypotheses 2001, V56, P388 HCAPLUS
(5) Chapman, P; Nat Neurosci 1999, V2, P271 HCAPLUS
(6) Chen, G; Nature (London) 2000, V408, P975 HCAPLUS
(7) Cimadevilla, J; Brain Res Bull 2001, V54, P559 MEDLINE
(8) Cimadevilla, J; Neurosci Lett 2000, V285, P53 HCAPLUS
(9) Dodart, J; Behav Neurosci 1999, V111, P982
(10) Duff, K; Curr Opin Biotechnol 1998, V9, P561 HCAPLUS
(11) Emere, M; Neurobiol Aging 1992, V13, P553
(12) Fiore, M; Behav Brain Res 2000, V112, P165 HCAPLUS
(13) Games, D; Nature (London) 1995, V373, P523 HCAPLUS
(14) Giulian, D; Neurochem Int 1995, V27, P119 HCAPLUS
(15) Gold, L; Adv Exp Med Biol 1996, V402, P199 HCAPLUS
(16) Gray, R; Nature (London) 1996, V383, P713 HCAPLUS
(17) Hartley, D; J Neurosci 1999, V19, P8876 HCAPLUS
(18) Higgins, G; Proc Natl Acad Sci USA 1990, V87, P3032 HCAPLUS
(19) Higgins, L; Ann Neurol 1994, V35, P598 MEDLINE
(20) Higgins, L; Mol Med Today 1999, V5, P274 MEDLINE
(21) Higgins, L; Proc Natl Acad Sci USA 1995, V92, P4402 HCAPLUS
(22) Holcomb, L; Behav Genet 1999, V29, P177 MEDLINE
(23) Holcomb, L; Nat Med 1998, V4, P97 HCAPLUS
(24) Hsiao, K; Prog Brain Res 1998, V117, P335 HCAPLUS
(25) Hsiao, K; Science 1996, V274, P99 HCAPLUS
(26) Irizarry, M; J Neurosci 1997, V17, P7053 HCAPLUS
(27) Janus, C; Biochim Biophys Acta 2000, V1502, P63 HCAPLUS
(28) Janus, C; Nature (London) 2000, V408, P979 HCAPLUS
(29) Janus, C; Neurobiol Aging 2000, V21, P541 HCAPLUS
(30) Kaminsky, Y; Physiol Res 1997, V46, P223 MEDLINE
(31) King, D; Behav Brain Res 1999, V103, P145 MEDLINE
(32) Lendon, C; J Am Med Assoc 1997, V277, P825 HCAPLUS
(33) Levin, E; Behav Pharmacol 1999, V10, P675 HCAPLUS
(34) Liu, Q; Proc Natl Acad Sci USA 2001, V98, P4734 HCAPLUS
(35) Lorenzo, A; Proc Natl Acad Sci USA 1994, V91, P12243 HCAPLUS
(36) Mattson, M; Neuron 1993, V10, P243 HCAPLUS
(37) McKee, A; Amyloid Int J Exp Clin Invest 1998, V5, P1 HCAPLUS
(38) Meyer, E; Brain Res 1997, V768, P49 HCAPLUS
(39) Milward, E; Neuron 1992, V9, P129 HCAPLUS
(40) Moran, P; Proc Natl Acad Sci USA 1995, V93, P5341
(41) Morgan, D; Nature (London) 2000, V408, P982 HCAPLUS
(42) Morris, R; J Neurosci Methods 1984, V11, P47 MEDLINE
(43) Motte, J; Acta Neuropathol 1989, V77, P535 MEDLINE
(44) Neve, R; Neuron 1988, V1, P669 HCAPLUS
(45) Pike, C; J Neurosci 1993, V13, P1676 HCAPLUS
(46) Price, D; Annu Rev Genet 1998, V32, P461 HCAPLUS
(47) Quon, D; Nature (London) 1991, V352, P239 HCAPLUS
(48) Saitoh, T; Cell 1989, V58, P615 HCAPLUS
(49) Selkoe, D; Nature (London) 1999, V399(Suppl), P23
(50) Shibuki, K; Eur J Neurosci 2001, V13, P609 MEDLINE
(51) Smith-Swintosky, V; J Neurochem 1994, V63, P781 HCAPLUS
(52) Takahashi, M; Neuron 2000, V28, P461 HCAPLUS
(53) Zhang, Z; Neuron 1996, V17, P1231 HCAPLUS
(54) Zhuo, M; Learn Mem 1998, V5, P467 MEDLINE

L34 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:824049 HCAPLUS
DN 133:346509
ED Entered STN: 24 Nov 2000

TI β -**Secretase** from human brain and HEK-293 cells and its use for screening drug modulators of β -**secretase** activity
IN Zhong, Ziyang; **Cordell, Barbara; Quon, Diana Hom; Liu, Yu-Wang**; Xu, Qiang
PA **Scios** Inc., USA; Eli Lilly and Company
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC A01N037-18; A01N043-04; A61K031-70; A61K038-00; C12N009-48; C12N009-64; C12Q001-37; G01N033-53; G01N033-537; G01N033-543
CC 7-2 (Enzymes)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000069262	A1	20001123	WO 2000-US13074	20000511
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2368624	AA	20001123	CA 2000-2368624	20000511
EP 1176871	A1	20020206	EP 2000-932358	20000511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002543815	T2	20021224	JP 2000-617730	20000511
US 2004132159	A1	20040708	US 2003-740865	20031218
PRAI US 1999-134074P	P	19990513		
US 2000-566746	A	20000509		
WO 2000-US13074	W	20000511		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000069262	IC	A01N037-18IC A01N043-04IC A61K031-70IC A61K038-00IC C12N009-48IC C12N009-64IC C12Q001-37IC G01N033-53IC G01N033-537IC G01N033-543
WO 2000069262	ECLA	C12N009/64F2C23; C12Q001/37
US 2004132159	NCL	435/226.000
	ECLA	C12N009/64F2C23; C12Q001/37

AB The invention concerns a novel β -**secretase**, a method of partially purifying this novel β -**secretase**, and its use in assays to screen for potential drug candidates against Alzheimer's disease and other neurol. diseases. The novel β -**secretase** has an estimated mol. weight of about 32-39 kDa or 22-26 kDa in HEK293 cell membrane exts. and human brain samples, resp., as calculated from radiation inactivation anal., and has a pH optimum at about pH 6.5-7.0.

ST secretase human characterization drug screening
IT Animal cell line
(Hek 293; β -**secretase** from human brain and HEK-293 cells and its use for screening drug modulators of β -**secretase** activity)
IT Cardiolipins
Phosphatidylinositols
Phosphatidylserines
Phospholipids, biological studies
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)

(stabilizer treatment prior to screening assays; β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

IT Brain
Drug screening
(β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

IT **Amyloid precursor proteins**
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

IT Antibodies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

IT **158736-49-3P**, β -Secretase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Abraham; US 5200339 A 1993 HCAPLUS
(2) Chrysler; US 5744346 A 1998 HCAPLUS
(3) Dovey; US 5424205 A 1995 HCAPLUS

L34 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:811590 HCAPLUS
DN 134:95421
ED Entered STN: 20 Nov 2000
TI Presenilin-1 and -2 are molecular targets for γ-secretase inhibitors
AU Seiffert, Dietmar; Bradley, Jodi D.; Rominger, Cynthia M.; Rominger, David H.; Yang, Fude; Meredith, Jere E., Jr.; Wang, Qian; Roach, Arthur H.; Thompson, Lorin A.; Spitz, Susan M.; Higaki, Jeffrey N.; Prakash, Shimoga R.; Combs, Andrew P.; Copeland, Robert A.; Arneric, Stephen P.; Hartig, Paul R.; Robertson, David W.; **Cordell, Barbara**; Stern, Andrew M.; Olson, Richard E.; Zaczek, Robert
CS DuPont Pharmaceuticals Company, Wilmington, DE, 19880, USA
SO Journal of Biological Chemistry (2000), 275(44), 34086-34091
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 1-11 (Pharmacology)
Section cross-reference(s): 7
AB Presenilins are integral membrane protein involved in the production of amyloid β-protein. Mutations of the presenilin-1 and -2 gene are associated with familial Alzheimer's disease and are thought to alter γ-secretase cleavage of the β-amyloid precursor protein, leading to increased production of longer and more amyloidogenic forms of Aβ, the 4-kDa β-peptide. Here, we show that radiolabeled γ-secretase inhibitors bind to mammalian cell membranes, and a benzophenone analog specifically photocross-links three major membrane polypeptides. A pos. correlation is observed among these compds. for inhibition of cellular Aβ formation, inhibition of membrane binding and crosslinking. Immunol. techniques establish N- and C-terminal

fragments of presenilin-1 as specifically cross-linked polypeptides. Furthermore, binding of γ-secretase inhibitors to embryonic membranes derived from presenilin-1 knockout embryos is reduced in a gene dose-dependent manner. In addition, C-terminal fragments of presenilin-2 are specifically cross-linked. Taken together, these results indicate that potent and selective γ-secretase inhibitors block Aβ formation by binding to presenilin-1 and -2.

ST secretase inhibitor membrane presenilin crosslinking

IT **Presenilins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1 and 2; presenilin-1 and -2 as mol. targets for γ-secretase inhibitors)

IT Cell membrane
Crosslinking
(presenilin-1 and -2 as mol. targets for γ-secretase inhibitors: cell membrane binding)

IT **158736-49-3**, γ-Secretase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(presenilin-1 and -2 as mol. targets for γ-secretase inhibitors)

IT 209986-17-4P 258864-62-9P 258864-67-4P 258864-68-5P 258864-80-1P 258870-13-2P 280568-31-2P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(presenilin-1 and -2 as mol. targets for γ-secretase inhibitors: cell membrane binding)

IT 76944-95-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(presenilin-1 and -2 as mol. targets for γ-secretase inhibitors: cell membrane binding)

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Beckett, R; Synlett 1993, V2, P137
(2) Capell, A; J Biol Chem 1998, V273, P3205 HCAPLUS
(3) Czech, C; Prog Neurobiol 2000, V60, P363 HCAPLUS
(4) De Strooper, B; Nature 1998, V391, P387 HCAPLUS
(5) De Strooper, B; Nature 1999, V402, P471 HCAPLUS
(6) Haass, C; Neuron 1997, V18, P687 HCAPLUS
(7) Haass, C; Science 1999, V286, P916 HCAPLUS
(8) Harlow, E; Using Antibodies: A Laboratory Manual 1999
(9) Herreman, A; Proc Natl Acad Sci U S A 1999, V96, P11872 HCAPLUS
(10) Higaki, J; J Med Chem 1999, V42, P3889 HCAPLUS
(11) Hooper, N; Biochem J 1997, V321, P265 HCAPLUS
(12) Hussain, I; Mol Cell Neurosci, www.academicpress.com/www/journal/cn/mence 1999
(13) Keen, M; Receptor Binding Techniques 1999, P106
(14) Laemmli, U; Nature 1970, V227, P680 HCAPLUS
(15) Lin, X; Proc Natl Acad Sci U S A 2000, V97, P1456 HCAPLUS
(16) Moore, C; Exp Opin Ther Patents 1999, V9, P135 HCAPLUS
(17) Selkoe, D; Annu Rev Cell Biol 1994, V10, P373 HCAPLUS
(18) Selkoe, D; Nature 1999, V399, PA23 HCAPLUS
(19) Sinha, S; Nature 1999, V402, P537 HCAPLUS
(20) Steiner, H; J Biol Chem 1999, V274, P28669 HCAPLUS
(21) Vassar, R; Science 1999, V286, P735 HCAPLUS
(22) Wolfe, M; Nature 1999, V398, P513 HCAPLUS
(23) Yan, R; Nature 1999, V402, P533 HCAPLUS
(24) Yu, G; J Biol Chem 1998, V273, P16470 HCAPLUS

L34 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:5300 HCAPLUS
DN 132:135959
ED Entered STN: 04 Jan 2000
TI Overexpression of the neuritotrophic cytokine S100β precedes the appearance of neuritic β-amyloid plaques in APPV717F mice
AU Sheng, J. G.; Mrak, R. E.; Bales, K. R.; **Cordell, B.**; Paul, S.

M.; Jones, R. A.; Woodward, S.; Zhou, X. Q.; McGinness, J. M.; Griffin, W. S. T.

CS Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

SO Journal of Neurochemistry (2000), 74(1), 295-301
CODEN: JONRA9; ISSN: 0022-3042
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)

AB Homozygous APPV717F transgenic mice overexpress a human β-amyloid precursor protein (**.beta.APP**) minigene encoding a familial Alzheimer's disease mutation. These mice develop Alzheimer-type neuritic β-amyloid plaques surrounded by astrocytes. S100β is an astrocyte-derived cytokine that promotes neurite growth and promotes excessive expression of **.beta.APP**. S100β overexpression in Alzheimer's disease correlates with the proliferation of **.beta.APP**-immunoreactive neurites in β-amyloid plaques. The authors found age-related increases in tissue levels of both **.beta.APP** and S100β mRNA in transgenic mice. Neuronal **.beta.APP** overexpression was found in cell somas in young mice, whereas older mice showed **.beta.APP** overexpression in dystrophic neurites in plaques. These age-related changes were accompanied by progressive increases in S100β expression, as determined by S100β load (percent immunoreactive area). These increases were evident as early as 1 and 2 mo of age, months before the appearance of β-amyloid deposits in these mice. Such precocious astrocyte activation and S100β overexpression are similar to the authors' earlier findings in Down's syndrome. Accelerated age-related overexpression of S100β may interact with age-associated overexpression of mutant **.beta.APP** in transgenic mice to promote development of Alzheimer-like neuropathol. changes.

ST neuritotrophic cytokine S100beta amyloid plaque

IT **Alzheimer's disease**
(familial; overexpression of neuritotrophic cytokine S100β precedes neuritic β-amyloid plaques development in model of)

IT Astrocyte
(neuritic β-amyloid plaques development is associated with S100β overexpression by)

IT Brain, disease
(senile plaque; overexpression of neuritotrophic cytokine S100β precedes neuritic β-amyloid plaques development in Alzheimer model)

IT **Amyloid**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β-; overexpression of neuritotrophic cytokine S100β precedes neuritic β-amyloid plaques development in Alzheimer model)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Barger, S; Nature 1997, V388, P878 HCAPLUS
(2) Buxbaum, J; Proc Natl Acad Sci 1992, V89, P10075 HCAPLUS
(3) da Cunha, A; Brain Res 1993, V600, P161 MEDLINE
(4) Esiri, M; J Neurol Neurosurg Psychiatry 1998, V65, P29 MEDLINE
(5) Games, D; Nature 1995, V373, P523 HCAPLUS
(6) Giulian, D; J Neurosci 1988, V8, P2485 HCAPLUS
(7) Griffin, W; Brain Pathol 1998, V8, P65 HCAPLUS
(8) Griffin, W; J Neurochem 1995, V65, P228 HCAPLUS
(9) Griffin, W; J Neurotrauma 1997, V15, P52
(10) Griffin, W; Neurobiol Aging 1998, V19, P401 HCAPLUS
(11) Griffin, W; Neurobiol Aging 1998, V19, P71 HCAPLUS
(12) Griffin, W; Neurosci Lett 1994, V176, P133 HCAPLUS
(13) Griffin, W; Proc Natl Acad Sci 1989, V86, P7611 MEDLINE
(14) Hof, P; Histol Histopathol 1996, V11, P1075 MEDLINE
(15) Kato, K; J Neurochem 1990, V54, P1269 HCAPLUS
(16) Kligman, D; Proc Natl Acad Sci 1985, V82, P7136 HCAPLUS
(17) Kowall, N; Neurobiol Aging 1992, V13, P537 HCAPLUS

(18) Li, Y; J Neurochem 1998, V71, P1421 HCAPLUS
(19) Mackenzie, I; Acta Neuropathol 1994, V87, P504 MEDLINE
(20) Marshak, D; Neurobiol Aging 1991, V13, P1
(21) Mayeux, R; Ann Neurol 1993, V33, P494 MEDLINE
(22) McKee, A; Amyloid Int J Exp Clin Invest 1998, V5, P1 HCAPLUS
(23) Mortimer, J; Int J Epidemiol 1991, V20(Suppl), PS28
(24) Mrak, R; J Neuropathol Exp Neurol 1996, V55, P273 MEDLINE
(25) Royston, M; Neuropathol Appl Neurobiol in press 1999
(26) Sheng, J; J Neurosci Res 1994, V39, P398 HCAPLUS
(27) Sheng, J; Neurobiol Aging 1996, V17, P359 HCAPLUS
(28) Sheng, J; Neurobiol Aging 1996, V17, P761 HCAPLUS
(29) Stanley, L; J Neuropathol Exp Neurol 1994, V53, P231 MEDLINE
(30) Stein-Behrens, B; Neurobiol Aging 1992, V13, P577 HCAPLUS
(31) Troncoso, J; Neurobiol Aging 1996, V17, P365 MEDLINE
(32) Van Eldik, L; Biochim Biophys Acta 1994, V1223, P298

L34 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:674911 HCAPLUS
DN 132:21804
ED Entered STN: 24 Oct 1999
TI Presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons
AU Annaert, Wim G.; Levesque, Lyne; Craessaerts, Kathleen; Dierinck, Inge; Snellings, Greet; Westaway, David; St. George-Hyslop, Peter; **Cordell, Barbara**; Fraser, Paul; De Strooper, Bart
CS CME/VIB4/KULeuven, Louvain, B-3000, Belg.
SO Journal of Cell Biology (1999), 147(2), 277-294
CODEN: JCLBA3; ISSN: 0021-9525
PB Rockefeller University Press
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB Mutations of presenilin 1 (PS1) causing Alzheimer's disease selectively increase the secretion of the amyloidogenic βA4(1-42), whereas knocking out the gene results in decreased production of both βA4(1-40) and (1-42) amyloid peptides (De Strooper,B.; et al., 1998). Therefore, PS1 function is closely linked to the γ-secretase processing of the amyloid precursor protein (APP). Given the ongoing controversy on the subcellular localization of PS1, it remains unclear at what level of the secretory and endocytic pathways PS1 exerts its activity on APP and on the APP carboxy-terminal fragments that are the direct substrates for γ-secretase. Therefore, we have reinvestigated the subcellular localization of endogenously expressed PS1 in neurons in vitro and in vivo using confocal microscopy and fine-tuned subcellular fractionation. We show that uncleaved PS1 holoprotein is recovered in the nuclear envelope fraction, whereas the cleaved PS fragments are found mainly in post-ER membranes including the intermediate compartment (IC). PS1 is concentrated in discrete sec23p- and p58/ERGIC-53-pos. patches, suggesting its localization in subdomains involved in ER export. PS1 is not found to significant amts. beyond the cis-Golgi. Surprisingly, we found that APP carboxy-terminal fragments also coenrich in the pre-Golgi membrane fractions, consistent with the idea that these fragments are the real substrates for γ-secretase. Functional evidence that PS1 exerts its effects on γ-secretase processing of APP in the ER/IC was obtained using a series of APP trafficking mutants. These mutants were investigated in hippocampal neurons derived from transgenic mice expressing PS1wt or PS1 containing clin. mutations (PS1M146L and PS1L286V) at physiol. relevant levels. We demonstrate that the APP-London and PS1 mutations have additive effects on the increased secretion of βA4(1-42) relative to βA4(1-40), indicating that both mutations operate independently. Overall, our data clearly establish that PS1 controls γ42-secretase activity in pre-Golgi compartments. We discuss models that reconcile this conclusion with the effects of PS1 deficiency on the generation of βA4(1-40) peptide in the late biosynthetic and endocytic pathways.
ST presenilin secretase amyloid precursor protein hippocampus neuron

IT **Presenilins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT Golgi apparatus
(cis-, presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT Cell nucleus
(envelope; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT **Alzheimer's disease**
(familial; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT Brain
(hippocampus; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT Nerve
(neuron; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT Organelle
(pre-Golgi compartment; presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT **Alzheimer's disease**
Endoplasmic reticulum
(presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT **Amyloid precursor proteins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT **107761-42-2**, Glycopeptide (human clone 9-110 amyloid A4 peptide moiety) **131438-79-4**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
IT **158736-49-3**, γ-Secretase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(presenilin 1 controls γ-secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
RE.CNT 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Annaert, W; J Cell Biol 1997, V139, P1397 HCAPLUS
(2) Arar, C; J Biol Chem 1995, V270, P3551 HCAPLUS
(3) Aridor, M; J Cell Biol 1998, V141, P61 HCAPLUS
(4) Bannykh, S; Histochem Cell Biol 1998, V109, P463 HCAPLUS
(5) Bannykh, S; J Cell Biol 1997, V138, P1 HCAPLUS
(6) Barlowe, C; Cell 1994, V77, P895 HCAPLUS
(7) Baumeister, R; Molecular Biology of Alzheimer's Disease 1998, P219 HCAPLUS
(8) Borchelt, D; Neuron 1996, V17, P1005 HCAPLUS
(9) Borchelt, D; Neuron 1997, V19, P939 HCAPLUS
(10) Brockhaus, M; Neuroreport 1998, V9, P1481 HCAPLUS
(11) Bu, G; Trends Cell Biol 1998, V8, P272 HCAPLUS
(12) Busciglio, J; J Neurosci 1997, V17, P5101 HCAPLUS
(13) Campbell, J; Proc Natl Acad Sci 1997, V94, P837 HCAPLUS
(14) Capell, A; J Biol Chem 1998, V273, P3205 HCAPLUS
(15) Capell, A; J Neurochem 1997, V69, P2432 HCAPLUS

(16) Chyung, A; J Cell Biol 1997, V138, P671 HCAPLUS
(17) Citron, M; Nat Med 1997, V3, P67 HCAPLUS
(18) Citron, M; Neurobiol Dis 1998, V5, P107 HCAPLUS
(19) Cook, D; Nat Med 1997, V3, P1021 HCAPLUS
(20) Cook, D; Proc Natl Acad Sci 1996, V93, P9223 HCAPLUS
(21) Cosson, P; Science 1994, V263, P1629 HCAPLUS
(22) Culvenor, J; J Neurosci Res 1997, V49, P719 HCAPLUS
(23) De Strooper, B; EMBO J 1995, V14, P4932 MEDLINE
(24) De Strooper, B; J Biol Chem 1997, V272, P3590 HCAPLUS
(25) De Strooper, B; J Cell Biol 1993, V121, P295 HCAPLUS
(26) De Strooper, B; Nature 1998, V391, P387 HCAPLUS
(27) De Strooper, B; Nature 1999, V398, P518 HCAPLUS
(28) Dewji, N; Proc Natl Acad Sci 1997, V94, P9926 HCAPLUS
(29) Doan, A; Neuron 1996, V17, P1023 HCAPLUS
(30) Duff, K; Nature 1996, V383, P710 HCAPLUS
(31) Dugan, J; J Biol Chem 1995, V270, P10982 HCAPLUS
(32) Efthimiopoulos, S; J Neurochem 1998, V71, P2365 HCAPLUS
(33) Evan, G; Mol Cell Biol 1985, V5, P3610 HCAPLUS
(34) Gorlich, D; Cell 1992, V71, P489 HCAPLUS
(35) Goslin, K; Culturing Nerve Cells 1991, P251
(36) Greenfield, J; Proc Natl Acad Sci 1999, V96, P742 HCAPLUS
(37) Haass, C; Cell 1993, V75, P1039 HCAPLUS
(38) Haass, C; Nat Med 1995, V1, P1291 HCAPLUS
(39) Hartmann, E; Eur J Biochem 1993, V214, P375 HCAPLUS
(40) Hartmann, T; Nat Med 1997, V3, P1016 HCAPLUS
(41) Higaki, J; Neuron 1995, V14, P651 HCAPLUS
(42) Johnston, J; J Cell Biol 1998, V143, P1883 HCAPLUS
(43) Klumperman, J; J Cell Sci 1998, V111, P3411 HCAPLUS
(44) Koo, E; J Biol Chem 1994, V269, P17386 HCAPLUS
(45) Kovacs, D; Nat Med 1996, V2, P224 HCAPLUS
(46) Krijnse-Locker, J; Mol Biol Cell 1995, V6, P1315 HCAPLUS
(47) Kuehn, M; Nature 1998, V391, P187 HCAPLUS
(48) Laemmli, U; Nature 1970, V227, P680 HCAPLUS
(49) Lah, J; J Neurosci 1997, V17, P1971 HCAPLUS
(50) Lahtinen, U; J Biol Chem 1996, V271, P4031 HCAPLUS
(51) Lehmann, S; J Biol Chem 1997, V272, P12047 HCAPLUS
(52) Levesque, L; Mol Med In press 1999
(53) Levey, A; Ann Neurol 1997, V41, P742 MEDLINE
(54) Levitan, D; Nature 1995, V377, P351 HCAPLUS
(55) Levy-Lahad, E; Science 1995, V269, P973 HCAPLUS
(56) Li, J; Cell 1997, V90, P917 HCAPLUS
(57) Li, X; Neuron 1996, V17, P1015 HCAPLUS
(58) Li, X; Proc Natl Acad Sci 1998, V95, P7109 HCAPLUS
(59) Liljestrom, P; Biotechnology 1991, V9, P1356 MEDLINE
(60) Maguire, G; FEBS Lett 1985, V180, P122 HCAPLUS
(61) Mercken, M; FEBS Lett 1996, V389, P297 HCAPLUS
(62) Naruse, S; Neuron 1998, V21, P1213 HCAPLUS
(63) Olkkonen, V; J Neurosci Res 1993, V35, P445 HCAPLUS
(64) Otto, H; Neurochem Int 1992, V21, P409 HCAPLUS
(65) Paganetti, P; J Neurosci Res 1996, V46, P283 HCAPLUS
(66) Peraus, G; J Neurosci 1997, V17, P7714 HCAPLUS
(67) Perez, R; J Biol Chem 1996, V271, P9100 HCAPLUS
(68) Perez, R; J Biol Chem 1999, V274, P18851 HCAPLUS
(69) Ratovitski, T; J Biol Chem 1997, V272, P24536 HCAPLUS
(70) Rogaev, E; Nature 1995, V376, P775 HCAPLUS
(71) Sambamurti, K; Ann NY Acad Sci 1992, V674, P118 HCAPLUS
(72) Saraste, J; J Cell Sci 1991, V100, P415 HCAPLUS
(73) Schekman, R; Science 1996, V271, P1526 HCAPLUS
(74) Scheuner, D; Nat Med 1996, V2, P864 HCAPLUS
(75) Schwarzman, A; Proc Natl Acad Sci 1999, V96, P7932 HCAPLUS
(76) Schweizer, A; Eur J Cell Biol 1990, V53, P185 HCAPLUS
(77) Schweizer, A; J Cell Biol 1991, V113, P45 HCAPLUS
(78) Selkoe, D; Trends Cell Biol 1998, V8, P447 HCAPLUS
(79) Sherrington, R; Nature 1995, V375, P754 HCAPLUS
(80) Simons, M; J Neurosci 1996, V16, P899 HCAPLUS
(81) Simons, M; J Neurosci Res 1995, V41, P121 HCAPLUS

(82) Sisodia, S; Proc Natl Acad Sci 1992, V89, P6075 HCAPLUS
(83) Steiner, H; J Biol Chem In press 1999
(84) Thinakaran, G; J Biol Chem 1997, V272, P28415 HCAPLUS
(85) Thinakaran, G; Molecular Biology of Alzheimer's Disease 1998, P193 HCAPLUS
(86) Thinakaran, G; Neuron 1996, V17, P181 HCAPLUS
(87) Tienari, P; Cold Spring Harbor Symp Quant Biol 1996, V61, P575 HCAPLUS
(88) Tienari, P; EMBO J 1996, V15, P5218 HCAPLUS
(89) Tomita, S; J Biol Chem 1998, V273, P6277 HCAPLUS
(90) Towbin, H; Proc Natl Acad Sci 1979, V76, P4350 HCAPLUS
(91) Weidemann, A; Nat Med 1997, V3, P328 HCAPLUS
(92) Wild-Bode, C; J Biol Chem 1997, V272, P16085 HCAPLUS
(93) Wolfe, M; Nature 1999, V398, P513 HCAPLUS
(94) Xia, W; Biochemistry 1998, V37, P16465 HCAPLUS
(95) Xia, W; Proc Natl Acad Sci 1997, V94, P8208 HCAPLUS
(96) Yamazaki, T; J Cell Biol 1995, V129, P431 HCAPLUS
(97) Zhang, L; J Biol Chem 1999, V274, P8966 HCAPLUS

L34 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:529819 HCAPLUS
DN 131:295102
ED Entered STN: 25 Aug 1999
TI A Combinatorial Approach to the Identification of Dipeptide Aldehyde Inhibitors of β-Amyloid Production
AU Higaki, Jeffrey N.; Chakravarty, Sarvajit; Bryant, Carmen M.; Cowart, Lisa R.; Harden, Paul; Scardina, Jan Marian; Mavunkel, Babu; Luedtke, Gregory R.; **Cordell, Barbara**
CS **Scios** Inc., Sunnyvale, CA, 94086, USA
SO Journal of Medicinal Chemistry (1999), 42(19), 3889-3898
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 13, 34
AB In an effort to rapidly identify potent inhibitors of Aβ production and to probe the amino acid sequence specificity of the protease(s) responsible for the production of this peptide, a large number of dipeptide aldehydes were combinatorially synthesized and manually evaluated for their inhibitory properties. The starting point for this study was the dipeptide aldehyde carbobenzoxyl-valinyl-phenylalanal previously shown to inhibit the production of Aβ in CHO cells stably transfected with the cDNA encoding **.beta.APP695**. Pools of related dipeptide aldehydes were combinatorially synthesized, and the most active pool was deconvoluted, resulting in the identification of the most active inhibitor of this pool. Systematic optimization of this inhibitor resulted in a series of dipeptide aldehydes with enhanced potencies relative to carbobenzoxyl-valinyl-phenylalanal. The most active dipeptide aldehydes were those that possessed hydrophobic amino acids at both the P1 and P2 positions. The most potent compound identified in this study was 3,5-dimethoxycinnamamide-isoleucinyl-leucinal with an IC50 of 9.6 μM, approx. 10-fold more active than carbobenzoxyl-valinyl-phenylalanal. In immunopptn. expts. using antibodies directed toward either Aβ1-40 or Aβ1-42, 3,5-dimethoxycinnamamide-isoleucinyl-leucinal, like carbobenzoxyl-valinyl-phenylalanal, preferentially inhibited the shorter 1-40 form of Aβ, whereas the longer 1-42 form was not as strongly inhibited. These results suggest that dipeptide aldehydes related to carbobenzoxyl-valinyl-phenylalanal inhibit Aβ through similar mechanisms and demonstrate the utility of a combinatorial synthesis approach to rapidly identify potent inhibitors of Aβ production
ST beta amyloid prodn dipeptide aldehyde structure; combinatorial dipeptide aldehyde library amyloid prodn; secretase beta amyloid prodn dipeptide aldehyde
IT Peptide library
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)
IT Aldehydes, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(peptide aldehydes; combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT **Amyloid**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(β-; combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT Structure-activity relationship
(β-amyloid production-inhibiting; combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT 88191-84-8 247021-87-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT 593-56-6 1663-39-4 28920-43-6, Fmoc-chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT 247021-88-1P 247021-89-2P 247021-90-5DP, conjugates with methoxybenzhydrylamine resin 247021-90-5DP, conjugates with methoxybenzhydrylamine resin
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

IT **158736-49-3**, γ-Secretase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β-amyloid production by; combinatorial approach to identification of dipeptide aldehyde inhibitors of β-amyloid production)

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Berger, A; Phil Trans R Soc London B 1970, V257, P249 HCAPLUS
(2) Busciglio, J; Proc Natl Acad Sci USA 1993, V90, P2092 HCAPLUS
(3) Caporaso, G; Proc Natl Acad Sci USA 1992, V89, P2252 HCAPLUS
(4) Citron, M; Neuron 1996, V17, P171 HCAPLUS
(5) Citron, M; Proc Natl Acad Sci USA 1996, V93, P13170 HCAPLUS
(6) Cook, D; Nature Med 1997, V3, P1021 HCAPLUS
(7) Esch, F; Science 1990, V248, P1122 HCAPLUS
(8) Estus, S; Science 1992, V255, P726 HCAPLUS
(9) Evin, G; Amyloid: Int J Exp Clin Invest 1994, V1, P263 HCAPLUS
(10) Fehrentz, J; Tetrahedron Lett 1995, V36, P7871 HCAPLUS
(11) Golde, T; Science 1992, V255, P728 HCAPLUS
(12) Gowing, E; J Biol Chem 1994, V269, P10987 HCAPLUS
(13) Haass, C; J Biol Chem 1993, V268, P3021 HCAPLUS
(14) Haass, C; Nature 1992, V357, P500 HCAPLUS
(15) Hamazaki, H; FEBS Lett 1998, V424, P136 HCAPLUS
(16) Hartmann, T; Nature Med 1997, V3, P1016 HCAPLUS
(17) Hayashi, Y; Biochem Biophys Res Commun 1992, V187, P1249 HCAPLUS
(18) Higaki, J; Neuron 1995, V14, P651 HCAPLUS
(19) Hodge, C; Antiviral Chem Chemother 1994, V5, P257 HCAPLUS
(20) Klafki, H; Anal Biochem 1996, V237, P24 HCAPLUS
(21) Klafki, H; J Biol Chem 1996, V271, P28655 HCAPLUS
(22) Koo, E; J Biol Chem V269, P17386 HCAPLUS
(23) Lichtenthaler, S; Biochemistry 1997, V36, P15396 HCAPLUS
(24) Lichtenthaler, S; Proc Natl Acad Sci USA 1999, V96, P3053 HCAPLUS
(25) McConnell, R; J Med Chem 1993, V36, P1084 HCAPLUS
(26) Murphy, G; Am J Pathol 1994, V144, P1082 HCAPLUS
(27) Nordstedt, C; J Biol Chem 1993, V268, P608 HCAPLUS
(28) Oltersdorf, T; J Biol Chem 1990, V265, P4492 HCAPLUS

(29) Parisi, M; Biochemistry 1992, V31, P9429 HCAPLUS
(30) Parvathy, S; Biochemistry 1998, V37, P1680 HCAPLUS
(31) Roberts, S; J Biol Chem 1994, V269, P3111 HCAPLUS
(32) Selkoe, D; Annu Rev Neurosci 1994, V17, P489 HCAPLUS
(33) Seubert, P; Nature 1993, V361, P260 HCAPLUS
(34) Shoji, M; Science 1992, V258, P126 HCAPLUS
(35) Siman, R; J Biol Chem 1993, V268, P16602 HCAPLUS
(36) Sisodia, S; Science 1990, V248, P492 HCAPLUS
(37) Suzuki, N; Science 1994, V264, P1336 HCAPLUS
(38) Thaisrivongs, S; J Med Chem 1986, V29, P2080 HCAPLUS
(39) Tieneri, P; Proc Natl Acad Sci USA 1997, V94, P4125
(40) Tischer, D; J Biol Chem 1996, V271, P21914
(41) Weidemann, A; Cell 1989, V57, P115 HCAPLUS
(42) Wild-Bode, C; J Biol Chem 1997, V272, P16085 HCAPLUS
(43) Wolf, D; EMBO J 1990, V9, P2079 HCAPLUS
(44) Wolfe, M; J Med Chem 1998, V41, P6 HCAPLUS
(45) Yamazaki, T; Biochemistry 1997, V36, P8377 HCAPLUS

L34 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:605021 HCAPLUS
DN 129:198885
ED Entered STN: 24 Sep 1998
TI Animal cell lines manufacturing β-amyloid and their use in the screening for drugs affecting its processing and accumulation
IN **Cordell, Barbara**; Scardina, Jan Marian; Mischak, Ronald P.; Huggins, John; Pruss, Rebecca; Rautmann, Guy
PA Hoechst Marion Roussel, Inc., USA; **Scios** Inc.
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-85
ICS C12N015-12; C12N005-10; C07K014-47; G01N033-68; C07K016-18
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9837215	A1	19980827	WO 1998-US1899	19980203
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9862600	A1	19980909	AU 1998-62600	19980203
	EP 973923	A1	20000126	EP 1998-904812	19980203
	R: CH, DE, FR, GB, IT, LI				
	JP 2001512973	T2	20010828	JP 1998-536647	19980203
	ZA 9801387	A	19980824	ZA 1998-1387	19980219
PRAI	US 1997-804971	A	19970224		
	US 1997-825737	A	19970402		
	US 1997-904296	A	19970731		
	WO 1998-US1899	W	19980203		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9837215	ICM	C12N015-85
	ICS	C12N015-12; C12N005-10; C07K014-47; G01N033-68; C07K016-18
WO 9837215	ECLA	C07K014/47A3

AB Eukaryotic cell lines useful in the identification of inhibitors of β-amyloid processing are designed and constructed. More specifically, the invention relates to in vitro assays capable of

identifying or quantifying a 4.2 kDa β-amyloid protein. A vector for high-level expression of a cDNA for the 695 amino acid isoform of amyloid precursor (APP695) was cloned and placed under control of the cytomegalovirus immediate-early promoter. CHO cells transformed with the expression construct were screened for high levels of production of APP695 and β-amyloid. High producers were further studied to identify the patterns of accumulation of processing products. Lines yielding ≥70 ng β-amyloid/mg protein were obtained. Characterization of patterns of processing can be used to identify agents affecting processing.

ST beta amyloid processing cells high yield; amyloid processing cells inhibitor screening

IT **Amyloid precursor proteins**
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(APP695, cloning and expression of cDNA for, processing of; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(CAD, as selectable marker; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Animal cell line
(CHO, expression host; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(IRES (internal ribosomal entry site) element, in expression construct for β-amyloid precursor; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT **Alzheimer's disease**
Animal cell line
Drug screening
(animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Kidney
(cell lines of human, as expression host; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Hamster
(cell lines of, as expression host; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Immunoassay
(enzyme-linked immunosorbent assay, for β-amyloid; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Encephalomyocarditis virus
(expression vectors using IRES element of; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(for β-amyloid precursor, cloning and expression of; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)

IT Neuroglia
(glioma, cell lines of, as expression host; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its

processing and accumulation)
IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(immediate early, APP695 cDNA expression from; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Antibodies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(monoclonal, to β-amyloid; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Nerve, neoplasm
(neuroblastoma, cell lines of, as expression host; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Post-translational processing
(of β-amyloid; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Plasmid vectors
(pCMV-IRES-β **APP695**, cDNA for amyloid precursor protein 695-amino acid isoform on; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT **Amyloid precursor proteins**
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(processing of; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Immunoassay
(radioimmunoassay, for β-amyloid; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT Antibodies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to β-amyloid; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT **Amyloid**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(β-; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT 3654-96-4, L-Methionine-35S 24321-12-8, L-Cysteine-35S
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(as label for monitoring of amyloid precursor processing; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
IT 9002-06-6, Thymidine kinase 9012-49-1, Aspartate transcarbamylase 9023-69-2, Asparagine synthase 9023-70-5, Glutamine synthase 9024-60-6, Ornithine decarboxylase 9026-93-1, Adenosine deaminase 37350-22-4, Xanthine-guanine phosphoribosyltransferase 56941-28-7, Aminoglycoside phosphotransferase 62213-36-9, Neomycin phosphotransferase 74870-74-9, UMP synthetase 88361-67-5, Hygromycin B phosphotransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for, as selectable marker; animal cell lines manufacturing β-amyloid and their use in screening for drugs affecting its processing and accumulation)
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cordell, B; US 5387742 A 1995 HCAPLUS
(2) Henriksson, T; JOURNAL OF NEUROCHEMISTRY 1991, V56(3), P1037 HCAPLUS

(3) Kang, J; NATURE 1987, V325, P733 HCAPLUS
(4) Kozak, M; NUCLEIC ACIDS RESEARCH 1987, V15(20), P8125 HCAPLUS
(5) Nabel, E; WO 9429469 A 1994 HCAPLUS
(6) Naidu, A; JOURNAL OF BIOLOGICAL CHEMISTRY 1995, V270(3), P1369 HCAPLUS
(7) Shoji, M; SCIENCE 1992, V258, P126 HCAPLUS

L34 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:239357 HCAPLUS
DN 128:278968
ED Entered STN: 27 Apr 1998
TI Method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase
IN **Cordell, Barbara**; Higaki, Jeffrey N.
PA **Scios** Inc., USA; Cordell, Barbara; Higaki, Jeffrey N.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-50
ICS G01N033-68
CC 1-1 (Pharmacology)
Section cross-reference(s): 9
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9815828	A1	19980416	WO 1997-US16988	19970919
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9745892	A1	19980505	AU 1997-45892	19970919
PRAI US 1996-726524	A	19961007		
WO 1997-US16988	W	19970919		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9815828	ICM	G01N033-50
	ICS	G01N033-68
WO 9815828	ECLA	G01N033/50D2; G01N033/68V2

AB A method for identifying direct inhibitors of γ-secretase is described. A cell line expressing β -**APP** is cultured in contact with a compound known to inhibit γ-secretase activity, thereby causing accumulation of β -**APP** carboxyl-terminal fragments in the cell. The known γ-secretase inhibiting compound is removed and replaced with a test substance. The direct γ-secretase inhibitory activity of the test substance is determined by quantifying the amount of β -**APP** carboxyl-terminal fragments in the cells and/or quantifying the amount of β-amyloid peptide in the culture medium over time.
ST gamma secretase inhibitor beta amyloid; Alzheimer beta amyloid gamma secretase inhibitor
IT Animal tissue culture
Anti-Alzheimer's agents
(method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)
IT **Amyloid**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β-; method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)
IT 88191-84-8, MDL 28170
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)
IT 158736-49-3, γ-Secretase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Higaki, J; NEURON 1995, V14, P651 HCAPLUS
(2) Ho, L; J BIOL CHEM 1996, V271(48), P30929 HCAPLUS
(3) Klafki, H; NEUROSCI LETT 1995, V201(1), P29 HCAPLUS
(4) McLean Hospital Corp; EP 0580161 A 1994 HCAPLUS
(5) Miles Inc; EP 0569777 A 1993 HCAPLUS
(6) Oriental Yeast Co Ltd; EP 0783104 A 1997 HCAPLUS

L34 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:21581 HCAPLUS
DN 126:155938
ED Entered STN: 15 Jan 1997
TI Processing of β-amyloid precursor protein by cathepsin D
AU Higaki, Jeffrey; Catalano, Rosanne; Guzzetta, Andrew W.; **Quon, Diana**; Nave, Jean-Francois; Tarnus, Celine; D'Orchymont, Hugues; **Cordell, Barbara**
CS **Scios**, Inc., Mountain View, CA, 94043, USA
SO Journal of Biological Chemistry (1996), 271(50), 31885-31893
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 7
AB The events leading to the formation of β-amyloid (βA4) from its precursor (**.beta.APP**) involve proteolytic cleavages that produce the amino and carboxyl termini of βA4. The enzyme activities responsible for these cleavages have been termed β- and γ-secretase, resp., although these protease(s) have not been identified. Since βA4 is known to possess heterogeneity at both the amino and carboxyl termini, β- and γ-secretases may actually be a collection of proteolytic activities or perhaps a single proteolytic enzyme with broad amino acid specificity. The authors investigated the role of cathepsin D in the processing of **.beta.APP** since this enzyme has been widely proposed as a γ-secretase candidate. Treatment of a synthetic peptide that spans the γ-secretase site of **.beta.APP** with human cathepsin D resulted in the cleavage of this substrate at Ala42-Thr43. A sensitive liquid chromatog./mass spectrometry technique was also developed to further investigate the ability of cathepsin D to process longer recombinant **.beta.APP** substrates (156 and 100 amino acids of **.beta.APP** carboxyl terminus) in vitro. The precise cathepsin D cleavage sites within these recombinant **.beta .APP** substrates were identified using this technique. Both recombinant substrates were cleaved at the following sites: Leu49-Val50, Asp68-Ala69, Phe93-Phe94. No cleavages were observed at putative γ-secretase sites: Val40-Ile41 or Ala42-Thr43, suggesting that cathepsin D is not γ-secretase as defined by these βA4 termini. Under conditions where the **.beta.APP156** substrate was first denatured prior to cathepsin D digestion, two addnl. cleavage sites near the amino terminus of βA4, Glu-3-Val-2 and Glu3-Phe4, were observed, indicating that cathepsin D cleavage of **.beta.APP** is influenced by the structural integrity of the substrate. Taken together, these results indicate that in vitro, cathepsin D is unlikely to function as γ-secretase; however, the ability of this enzyme to efficiently cleave **.beta.APP** substrates at nonamyloidogenic sites within the mol. may reflect a role in **.beta**

.APP catabolism.

ST beta amyloid precursor protein cathepsin D; Alzheimer beta amyloid precursor cathepsin D

IT **Alzheimer's disease**
Protein degradation
(processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT **Amyloid precursor proteins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT **Amyloid**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(β-; processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT 106096-93-9DP, Basic fibroblast growth factor, fusion protein with β-amyloid precursor protein APP751 and FLAG peptide 186795-27-7P 186847-25-6P
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of; processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT 148125-60-4DP, Proteinase inhibitor, protease-nexin II, fusion protein with FLAG peptide and basic fibroblast growth factor
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of; processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT 186847-24-5P
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of; processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT 9025-26-7, Cathepsin D
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

IT **158736-49-3**, γ-Secretase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(processing of β-amyloid precursor protein by human cathepsin D in relation to γ-secretase)

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Azaryan, A; Biomed Biochim Acta 1983, V10, P1237
(2) Brown, A; J Neurochem 1996, V66, P2436 HCAPLUS
(3) Busciglio, J; Proc Natl Acad Sci U S A 1993, V90, P2092 HCAPLUS
(4) Caporaso, G; Proc Natl Acad Sci U S A 1992, V89, P2252 HCAPLUS
(5) Cataldo, A; Neuron 1995, V14, P671 HCAPLUS
(6) Cataldo, A; Proc Natl Acad Sci U S A 1990, V87, P3861 HCAPLUS
(7) Cataldo, A; Proc Natl Acad Sci U S A 1991, V88, P10998 HCAPLUS
(8) Citron, M; Neuron 1995, V14, P661 HCAPLUS
(9) Cowburn, R; Trends Neurosci 1995, V18, P483 HCAPLUS
(10) Diment, S; J Biol Chem 1988, V263, P6901 HCAPLUS
(11) Dreyer, R; Eur J Biochem 1994, V224, P265 HCAPLUS
(12) Esch, F; Science 1990, V248, P1122 HCAPLUS
(13) Estus, S; Science 1992, V255, P726 HCAPLUS
(14) Evin, G; Biochemistry 1995, V34, P14185 HCAPLUS
(15) Evin, G; Int J Exp Clin Invest 1994, V1, P263 HCAPLUS
(16) Glenner, G; Biochem Biophys Res Commun 1984, V120, P885 HCAPLUS
(17) Golde, T; Science 1992, V255, P728 HCAPLUS
(18) Gulnick, S; J Mol Biol 1992, V227, P265

(19) Haass, C; J Biol Chem 1993, V268, P3021 HCAPLUS
(20) Haass, C; Nature 1992, V359, P322 HCAPLUS
(21) Haass, C; Nature 1992, V357, P500 HCAPLUS
(22) Hardy, J; Clin Geriatr Med 1994, V10, P239 MEDLINE
(23) Hayashi, Y; Biochem Biophys Res Commun 1992, V187, P1249 HCAPLUS
(24) Higaki, J; Neuron 1995, V14, P651 HCAPLUS
(25) Iwatsubo, T; Neuron 1994, V13, P45 HCAPLUS
(26) Kenessey, A; J Neurosci Res 1989, V23, P454 HCAPLUS
(27) Koo, E; J Biol Chem 1994, V269, P17386 HCAPLUS
(28) Ladror, U; J Biol Chem 1994, V269, P18422 HCAPLUS
(29) Lansbury, P; Arzneimittelforschung 1995, V45, P432 HCAPLUS
(30) Mantle, D; J Neurol Sci 1995, V131, P65 MEDLINE
(31) Marks, N; Int J Pept Protein Res 1995, V46, P306 HCAPLUS
(32) Masters, C; Proc Natl Acad Sci U S A 1985, V82, P4245 HCAPLUS
(33) Miller, D; Arch Biochem Biophys 1993, V301, P41 HCAPLUS
(34) Munger, J; Biochem J 1995, V311, P299 HCAPLUS
(35) Nakanishi, H; Exp Neurol 1994, V126, P119 HCAPLUS
(36) Nordstedt, C; J Biol Chem 1993, V268, P608 HCAPLUS
(37) Oltersdorf, T; J Biol Chem 1990, V265, P4492 HCAPLUS
(38) Runquist, E; J Biol Chem 1991, V266, P22557 HCAPLUS
(39) Schenk, D; J Med Chem 1995, V38, P4141 HCAPLUS
(40) Seubert, P; Nature 1992, V359, P325 HCAPLUS
(41) Seubert, P; Nature 1993, V361, P260 HCAPLUS
(42) Shoji, M; Science 1992, V258, P126 HCAPLUS
(43) Siman, R; J Biol Chem 1993, V268, P16602 HCAPLUS
(44) Sisodia, S; Science 1990, V248, P492 HCAPLUS
(45) Tischer, E; J Biol Chem 1996, V271, P21914 HCAPLUS
(46) van Noort, J; J Biol Chem 1989, V264, P14159 HCAPLUS
(47) Weidemann, A; Cell 1989, V57, P115 HCAPLUS
(48) Williams, K; Arch Biochem Biophys 1993, V305, P298 HCAPLUS
(49) Wisniewski, T; Ann Neurol 1994, V35, P245 MEDLINE
(50) Wolf, D; EMBO J 1990, V9, P2079 HCAPLUS
(51) Zhong, Z; J Biol Chem 1994, V269, P12179 HCAPLUS
(52) Zhong, Z; J Biol Chem 1994, V269, P627 HCAPLUS

L34 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:556391 HCAPLUS
DN 125:244059
ED Entered STN: 18 Sep 1996
TI β-Amyloid precursor protein. Location of transmembrane domain and specificity of γ-secretase cleavage
AU Tischer, Edmund; **Cordell, Barbara**
CS **Scios** Inc., Mountain View, CA, 94043, USA
SO Journal of Biological Chemistry (1996), 271(36), 21914-21919
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 6
AB The formation of β-amyloid by processing of its precursor protein is a characteristic of Alzheimer's disease. Two proteolytic cleavages produce the amino and carboxyl termini of β-amyloid, with the latter cleavage site located within the transmembrane domain. Using DNA mutagenesis, the authors investigated the membrane position and sequence requirements for carboxyl-terminal processing of the β-amyloid domain. Substitution of neg. charged residues across positions 40-46 of the β-amyloid domain precluded both β-amyloid formation and precursor maturation associated with secretory protein transport. In contrast, identical substitutions from positions 48-50 had no adverse effects. Since charged residues typically prevent protein membrane insertion, these data define the membrane boundary to position 46/47, a location allowing greater access to carboxyl-terminal processing of β-amyloid, possibly without membrane destruction. Deletions within the carboxyl-terminal domain, including 4 residues spanning positions 39-42 of β-amyloid, resulted in formation of the β-amyloid

peptide. Substituting residues 38-47 or 39-56 or the β-amyloid domain in the precursor with a transmembrane sequence from another protein yielded a .apprx.4kDa β-amyloid peptide, reflecting a loose residue specificity for carboxyl-terminal processing to β-amyloid.

ST beta amyloid precursor protein processing secretase

IT Protein sequences
(in β-amyloid precursor protein transmembrane domain for γ-secretase cleavage)

IT Molecular structure-biological activity relationship
(β-amyloid precursor protein transmembrane domain and specificity of γ-secretase cleavage in relation to β-amyloid formation)

IT Mental disorder
(Alzheimer's disease, β-amyloid precursor protein transmembrane domain and specificity of γ-secretase cleavage in relation to β-amyloid formation)

IT **Proteins, specific or class**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**amyloid A4**, β-amyloid precursor protein transmembrane domain and specificity of γ-secretase cleavage in relation to β-amyloid formation)

IT **Glycoproteins, specific or class**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**amyloid A4, pre-**, β-amyloid precursor protein transmembrane domain and specificity of γ-secretase cleavage in relation to β-amyloid formation)

IT **158736-49-3**, γ-Secretase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(β-amyloid precursor protein transmembrane domain and specificity of γ-secretase cleavage in relation to β-amyloid formation)

L34 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:208278 HCAPLUS
DN 124:285462
ED Entered STN: 11 Apr 1996
TI A model of β-amyloid formation and Alzheimer's disease
AU **Cordell, Barbara**; Higgins, Linda S.; Higaki, Jeffrey; Zhong, Ziyang; Moran, Paula M.; Moser, Paul M.
CS **Scios** Nova Inc., Mountain View, CA, 94043, USA
SO Alzheimer's Research (1995), 1(3), 111-15
CODEN: ALREFB; ISSN: 1356-918X
PB Rapid Science Publishers
DT Journal; General Review
LA English
CC 14-0 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 13
AB A review with 25 refs. The influence of a single gene can be evaluated in vitro and in vivo through mol. genetics. The authors have applied this approach to study β-amyloid formation and Alzheimer's disease. The gene under exptl. assessment was that encoding the human β-amyloid precursor protein (β -**APP**). The authors examined the pathol. influence of β -**APP** gene expression in cultured mammalian cells and transgenic mice. From the in vitro studies, the authors found that increased β-amyloid formation was associated with increased expression of β -**APP** and/or aberrant . **beta.-APP** mols. Hence, the authors hypothesized that β-amyloid is a minor degradative byproduct of β -**APP** catabolism. This hypothesis was exptl. supported at the in vivo level using transgenesis. Transgenic mice aberrantly expressing . **beta.-APP** in their neurons were shown to display histol. and behavioral features analogous to those observed in early Alzheimer's disease. These features included extracellular diffuse deposits of β-amyloid derived from the exogenous gene, aberrancies in the neuronal cytoskeleton, as well as memory and learning impairments. The

phenotype of this transgenic mouse indicates a central role for . **beta.-APP** in the pathogenesis of Alzheimer's disease and supports the hypothesis of β-amyloid formation.
ST review beta amyloid formation Alzheimer disease
IT Mouse
(transgenic; β-amyloid formation in pathogenesis of Alzheimer's disease using transgenic mouse model)
IT Mental disorder
(Alzheimer's disease, β-amyloid formation in pathogenesis of Alzheimer's disease using transgenic mouse model)
IT **Proteins, specific or class**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**amyloid A4**, β-amyloid formation in pathogenesis of Alzheimer's disease using transgenic mouse model)
IT Transformation, genetic
(transgenic, β-amyloid formation in pathogenesis of Alzheimer's disease using transgenic mouse model)

L34 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:617282 HCAPLUS
DN 123:53503
ED Entered STN: 16 Jun 1995
TI Age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein
AU Moran, Paula M.; Higgins, Linda S.; **Cordell, Barbara**; Moser, Paul C.
CS Marion Merrell Dow Research Inst., Strasbourg, 67080, Fr.
SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(12), 5341-5
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB The β-amyloid precursor protein (β -**APP**), from which the β-A4 peptide is derived, is considered to be central to the pathogenesis of Alzheimer disease (AD). Transgenic mice expressing the 751-amino acid isoform of human β -**APP** (. **beta.-APP751**) have been shown to develop early AD-like histopathol. with diffuse deposits of β-A4 and aberrant tau protein expression in the brain, particularly in the hippocampus, cortex, and amygdala. The authors now report that β -**APP751** transgenic mice exhibit age-dependent deficits in spatial learning in a water-maze task and in spontaneous alternation in a Y maze. These deficits were mild or absent in 6-mo-old transgenic mice but were severe in 12-mo-old transgenic mice compared to age-matched wild-type control mice. No other behavioral abnormalities were observed These mice therefore model the progressive learning and memory impairment that is a cardinal feature of AD. These results provide evidence for a relation between abnormal expression of β -**APP** and cognitive impairments.
ST amyloid precursor protein 751 Alzheimer disease
IT Brain
Senescence
(age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein)
IT Mental disorder
(Alzheimer's disease, age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein)
IT Learning
Memory, biological
(disorder, age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein)

IT Behavior
(spontaneous alternation, age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein)
IT 148125-60-4, Glycoproteins, specific or class, amyloid A4751
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β-amyloid precursor protein)

L34 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:562704 HCAPLUS
DN 123:30662
ED Entered STN: 20 May 1995
TI Early Alzheimer disease-like histopathology increases in frequency with age in mice transgenic for β -**APP751**
AU Higgins, L. S.; Rodems, J. M.; Catalano, R.; **Quon, D.**; **Cordell, B.**
CS **Scios** Nova Inc., Mountain View, CA, 94043, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(10), 4402-6
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB β-Amyloid deposition and neurofibrillary tangle formation are 2 histopathol. features of Alzheimer disease. The authors previously reported that β-amyloid immunoreactive deposits form in the brains of transgenic mice programmed for neuronal expression of the 751-amino acid isoform of human β-amyloid precursor protein (β -**APP751**) and now describe that these animals also display Alz50 intraneuronal immunoreactivity similar to that seen in early Alzheimer disease. This suggests that abnormal β -**APP** expression and/or β-amyloid deposition promotes pathogenic alterations in tau protein. The frequency of both β-amyloid deposition and Alz50-pos. neurons was twice as prevalent in brains from old (22 mo) as compared to young (2-3 mo) β -**APP751** transgenic mice. This increase in histopathol. with age in **.beta** .-**APP751** transgenic mice parallels the time-dependent progression seen in the human disease.
ST amyloid Alz50 Tau Alzheimer transgenic mouse
IT **Senescence**
(Alzheimer disease-like histopathol. increases in frequency with age in mice transgenic for β -**APP751**)
IT Glycoproteins, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(amyloid A4751; β-amyloid deposits and Alz50-pos. neurons of β -**APP751** transgenic mice increase with age)
IT **Tau factors**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β-amyloid deposits and Alz50-pos. neurons in β -**APP751** transgenic mice increase with age)
IT Antigens
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Alz-50, β-amyloid deposits and Alz50-pos. neurons in β -**APP751** transgenic mice increase with age)
IT Mental disorder
(Alzheimer's disease, β-amyloid deposits and Alz50-pos. neurons in β -**APP751** transgenic mice increase with age)
IT **Proteins, specific or class**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**amyloid A4**, β-amyloid deposits and Alz50-pos. neurons of β -**APP751** transgenic mice increase with age)
IT **Brain, disease**

(**neurofibrillary tangle**, β-amyloid deposits and Alz50-pos. neurons in β -**APP751** transgenic mice increase with age)

IT Brain, disease
(senile plaque, β-amyloid deposits and Alz50-pos. neurons in β -**APP751** transgenic mice increase with age)

L34 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:483374 HCAPLUS
DN 122:236925
ED Entered STN: 12 Apr 1995
TI Inhibition of β-amyloid formation identified proteolytic precursors and subcellular site of catabolism
AU Higaki, Jeffrey; **Quon, Diana**; Zhong, Ziyang; **Cordell, Barbara**
CS **Scios** Nova, Inc., Mountain View, CA, 94043, USA
SO Neuron (1995), 14(3), 651-9
CODEN: NERNET; ISSN: 0896-6273
PB Cell Press
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB Cerebral deposition of β-amyloid protein is a pathol. feature central to Alzheimer's disease. Production of β-amyloid by proteolytic processing of the β-amyloid precursor protein (β **APP**) is a critical initial step in β-amyloidogenesis. We use an inhibitor of **.beta.APP** processing to block β-amyloid peptide formation. Application of the inhibitor to cultured cells results in an accumulation of proteolytic intermediates of **.beta.APP**, enabling a precursor-product relationship between **.beta.APP** carboxy-terminal fragments and β-amyloid peptides to be demonstrated directly. In the presence of inhibitor, these amyloidogenic carboxy-terminal fragments can be degraded to nonamyloidogenic products. The catabolism of β **APP** carboxy-terminal intermediates and the formation of β-amyloid peptides are likely to involve an early endosomal compartment as the subcellular site of processing.
ST beta amyloid precursor protein endosome catabolism; Alzheimer disease beta amyloid accumulation
IT Down's syndrome
(catabolism of β-amyloid precursor protein in endosomal compartment results in β-amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)
IT Mental disorder
(Alzheimer's disease, catabolism of β-amyloid precursor protein in endosomal compartment results in β-amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)
IT **Proteins, specific or class**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**amyloid A4**, catabolism of β-amyloid precursor protein in endosomal compartment results in β-amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)
IT **Glycoproteins, specific or class**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**amyloid A4, pre-**, catabolism of β-amyloid precursor protein in endosomal compartment results in β-amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)
IT Organelle
(endocytic vesicle, catabolism of β-amyloid precursor protein in endosomal compartment results in β-amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

L34 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:480134 HCAPLUS
DN 121:80134
ED Entered STN: 20 Aug 1994
TI Increased amyloid production from aberrant β-amyloid precursor proteins
AU Zhong, Ziyang; **Quon, Diana**; Higgins, Linda S.; Higaki, Jeffrey; **Cordell, Barbara**
CS **Scios** Nova Inc., Mountain View, CA, 94043, USA
SO Journal of Biological Chemistry (1994), 269(16), 12179-84
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 13
AB The 4-kDa β-amyloid protein that forms fibrillar deposits in Alzheimer's diseased brains is derived from a large precursor, the β-amyloid precursor protein (β -**APP**). Recently, it has been reported that β-amyloid is normally produced and secreted by cultured mammalian cells. In the authors' studies involving recombinant expression of β -**APP**, increased yields of β-amyloid were associated with expression of aberrant β -**APP** mols. Deletion mutations within the β-amyloid domain, incorrect β -**APP** isoform expression in fibroblasts or neuronal cells, or excess amts. of . **beta.-APP** all led to increases in β-amyloid production Aberrant β -**APP** appears to be diverted from the secretory pathway and then degraded to β-amyloid.
ST aberrant beta amyloid precursor processing Alzheimer
IT Fibroblast
Nerve, metabolism
(aberrant β-amyloid precursor proteins of, β-amyloid protein formation response to)
IT Mental disorder
(Alzheimer's disease, β-amyloid formation from aberrant β-amyloid precursor proteins in relation to, in fibroblasts and neuron cells)
IT **Proteins, specific or class**
RL: FORM (Formation, nonpreparative)
(**amyloid A4**, formation of, fibroblasts and neuronal cell aberrant β-amyloid precursor proteins stimulation of)
IT **Glycoproteins, specific or class**
RL: BIOL (Biological study)
(**amyloid A4, pre-**, aberrant forms of, in fibroblasts and neuronal cells, β-amyloid protein formation response to)

L34 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:74682 HCAPLUS
DN 120:74682
ED Entered STN: 19 Feb 1994
TI Secretion of β-amyloid precursor protein involves multiple cleavage sites
AU Zhong, Ziyang; Higaki, Jeffrey; Murakami, Kenji; Wang, Yu; Catalano, Rosanne; **Quon, Diana**; **Cordell, Barbara**
CS **Scios** Nova Inc., Mountain View, CA, 94043, USA
SO Journal of Biological Chemistry (1994), 269(1), 627-32
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB A major histopathol. feature of Alzheimer's disease is deposition of a .apprx.4-kDa β-amyloid peptide derived by proteolytic processing from a precursor, the β-amyloid precursor protein (β -**APP**). Proteolytic cleavage of β -**APP**

within the .apprx.4-kDa β-amyloid domain permits the secretion of the amino-terminal portion of β -**APP** while concomitantly producing a membrane bound .apprx.9-kDa carboxyl-terminal fragment. The authors have characterized the proteolytic cleavage site for β -**APP** secretion by amino acid sequence anal. of the .apprx.9-kDa β -**APP** carboxyl-terminal cleavage product produced by recombinant and native expression systems. Recombinant β -**APP** was generated by a vaccinia virus expression system in CV-1 monkey fibroblasts; endogenous . **beta.-APP** was obtained using a fibroblast line derived from an individual with Down's syndrome. The sequences of both unlabeled and metabolically radiolabeled .apprx.9-kDa fragment from CV-1 cells reveal that the major (60%) secretory cleavage site is after Lys16 of the β-amyloid domain as reported previously; however, an addnl. cleavage site is seen after Phe19 (40%). Radiosequence anal. of the carboxyl-terminal fragment purified from Down's syndrome fibroblasts indicates cleavage sites after Phe19, Glu22, and Gly25 and not after Lys16. CV-1 cells expressing β -**APP** mutants lacking 4 and 6 amino acids adjacent to Lys16 yielded .apprx.9-kDa fragments with two identical cleavage sites, neither of which occurred after the retained Lys16 but were after Glu11 and His13. These data suggest that secretion of β -**APP** involves multiple proteinases and that the composition of these proteinases may vary within different cell backgrounds.

ST amyloid precursor protein processing proteinase Alzheimer

IT Mental disorder
(Alzheimer's disease, β-amyloid precursor protein processing by multiple proteinases and cleavage site identification in relation to)

IT **Glycoproteins, specific or class**
RL: BIOL (Biological study)
(**amyloid A4, pre-**, processing of, by multiple proteinases, cleavage site identification in, Alzheimer's disease in relation to)

IT 9001-92-7, Proteinase
RL: BIOL (Biological study)
(β-amyloid precursor protein processing by, cleavage site identification in, Alzheimer's disease in relation to)

L34 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:676982 HCAPLUS
DN 115:276982
ED Entered STN: 27 Dec 1991
TI Alzheimer's disease: β-amyloid precursor protein expression in plaques varies among cytoarchitectonic areas of the medial temporal lobe
AU Murphy, Greer M., Jr.; Murphy, Erin; Greenberg, Barry D.; **Cordell, Barbara**; Eng, Lawrence F.; Ellis, William G.; Forno, Lysia S.; Salamat, Shahriar M.; Gonzalez-DeWhitt, Patricia A.; et al.
CS Sch. Med., Stanford Univ., Palo Alto, CA, 94304, USA
SO Neuroscience Letters (1991), 131(1), 100-4
CODEN: NELED5; ISSN: 0304-3940
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB The anat. distributions of β-amyloid peptide (βAP) and β-amyloid precursor protein (**.beta.APP**) in the medial temporal lobe were examined with immunocytochem. in Alzheimer's disease. βAP-containing plaques were found most frequently in the cortical and basal regions of the amygdala, and in the hippocampal CA1, subiculum, and dentate mol. layer. **.beta.APP** expression in plaques was found in a similar distribution, with some, but not all βAP plaques also showing **.beta.APP**. In the cortical and basal amygdala, some cases showed β **APP** in the centers of plaques, whereas in the hippocampus, all cases displayed **.beta.APP** mainly in plaque neurites. The lateral regions of the amygdala contained mainly diffuse βAP plaques which had little **.beta.APP**. These findings

suggest that although .beta.APP expression and βAP deposition generally co-localize, processing of β APP may vary among closely interconnected anat. regions.
ST amyloid precursor protein plaque brain Alzheimer
IT Mental disorder
(Alzheimer's disease, β-amyloid precursor protein of neuritic plaques of brain regions in, of humans)
IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(amyloid A4, pre-, of neuritic plaques, of brain regions, in Alzheimer's disease of humans)
IT Brain, composition
(neuritic plaque, β-amyloid precursor protein of, in Alzheimer's disease of humans)

L34 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:512097 HCAPLUS
DN 115:112097
ED Entered STN: 23 Sep 1991
TI Formation of β-amyloid protein deposits in brains of transgenic mice
AU Quon, D.; Wang, Y.; Catalano, R.; Scardina, J. Marian; Murakami, K.; Cordell, B.
CS California Biotechnol. Inc., Mountain View, CA, 94043, USA
SO Nature (London, United Kingdom) (1991), 352(6332), 239-41
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB Deposits of β-amyloid are one of the main pathol. characteristics of Alzheimer's disease. The β-amyloid peptide constituent (relative mol. mass 4,200) of the deposits is derived from the β-amyloid precursor protein (β -APP) which is expressed in several different isoforms. The two most prevalent β -APP isoforms are distinguished by either the presence (. beta.-APP751) or absence (β -APP695) of a Kunitz serine protease inhibitor domain. Changes in the abundance of different β -APP mRNAs in brains of Alzheimer's disease victims have been widely reported. Although these results have been controversial, most evidence favors an increase in the mRNAs encoding protease inhibitor-containing isoforms of B-APP and it is proposed that this change contributes to B-amyloid formation. The authors have now produced an imbalance in the normal neuronal ratio of . beta.-APP isoforms by preparing transgenic mice expressing addnl. β -APP751 under the control of a neural-specific promoter. The cortical and hippocampal brain regions of the transgenic mice display extracellular β-amyloid immunoreactive deposits varying in size (<5-50 μm) and abundance. These results suggest that one mechanism of β-amyloid formation may involve a disruption of the normal ratio of neuronal β -APP isoform expression and support a direct relationship between increased expression of Kunitz inhibitor-bearing β -APP isoforms and β-amyloid deposition.
ST amyloid A4 isoform imbalance brain Alzheimer
IT Brain, composition
(β-amyloid deposition in, amyloid A4 isoform imbalance in, in Alzheimer's disease)
IT Mental disorder
(Alzheimer's disease, amyloid A4 isoform imbalance in brain β-amyloid deposition in)
IT Proteins, specific or class
RL: BIOL (Biological study)
(amyloid A4, brain deposits of, amyloid A4 isoform imbalance in, in Alzheimer's disease)
IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(amyloid A4695, imbalance in amyloid A4751 and, in

brain β-amyloid deposition in Alzheimer's disease)
IT Proteins, specific or class
RL: BIOL (Biological study)
(amyloid A4751, imbalance in amyloid A4695 protein and, in brain β-amyloid deposition in Alzheimer's disease)

L34 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:427110 HCAPLUS
DN 115:27110
ED Entered STN: 27 Jul 1991
TI Synthesis and characterization of the Kunitz protease-inhibitor domain of the β-amyloid precursor protein
AU Schilling, James; Wang, Yu; Lau, Ken; Smith, Leanne; **Cordell, Barbara**
CS California Biotechnol. Inc., Mountain View, CA, 94043, USA
SO Gene (1991), 98(2), 225-30
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB To understand the pathol. process by which amyloid is deposited in Alzheimer's disease, it is important to characterize the proteolytic processing events of the β-amyloid precursor protein (**.beta .-APP**) from which the amyloid-forming fragment is excised. A potentially important component in β **-APP** processing is the 57-amino acid (aa) Kunitz serine protease inhibitor (KPI) located within the extracellular domain of both the 751- and 770-aa isoforms of β **-APP.** The authors have synthesized DNA encoding the 57-aa KPI domain as a necessary step in identifying the role of the protease inhibitor in β **-APP** processing and amyloid formation. A bacterial secretion system directed by the alkaline phosphatase signal peptide of Escherichia coli linked to a synthetic gene encoding KPI was used to produce soluble, extracellular recombinant KPI (reKPI) protein. The reKPI protein was purified to homogeneity from bacterial supernatants and was biochem. and biol. characterized. Complete aa sequence anal. confirmed the fidelity of the reKPI, and fast-atom bombardment mass-spectral anal. was used to document that reKPI was of the predicted Mr. The reKPI is as active on a molar basis as the inhibitor-containing β **-APP** when assayed for inhibition of trypsin activity. Together these data suggest that reKPI protein is properly folded and lacking in modified aa. Hence, this reKPI will be an important reagent in gaining a better understanding of the role of the KPI domain in β **-APP** function and metabolism, as well as in the proteolytic events involved in β-amyloid formation.
ST Kunitz protease inhibitor amyloid precursor protein
IT Protein sequences
(for β-amyloid precursor protein Kunitz protease inhibitor domain, Alzheimer's disease pathogenesis in relation to)
IT Mental disorder
(Alzheimer's disease, pathogenesis of, β-amyloid precursor protein processing in, formation and characterization of recombinant Kunitz protease-inhibitor domain of β-amyloid precursor protein in relation to)
IT **Glycoproteins, specific or class**
RL: PRP (Properties)
(amyloid A4, pre-, formation and characterization of recombinant Kunitz protease-inhibitor domain of, Alzheimer's disease pathogenesis in relation to)
IT 117312-67-1, 289-345-Glycoprotein (human clone λAPCP168i4 amyloid A4 precursor protein moiety reduced)
RL: BIOL (Biological study)
(recombinant, amino acid sequence of, Alzheimer's disease pathogenesis in relation to)

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=> d all l43 tot


L43  ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:176537  HCAPLUS
DN   140:231420
ED   Entered STN:  04 Mar 2004
TI   Protein and cDNA sequences of a novel human β -
     secretase and use in screening drugs for treating Alzheimer's
     disease
IN   Gurney, Mark E.; Bienkowski, Michael J.; Heinrikson, Robert L.; Parodi,
     Luis A.; Yan, Riqiang
PA   Pharmacia & Upjohn Company, USA
SO   U.S., 103 pp., Cont.-in-part of U.S. Ser. No. 404,133, abandoned.
     CODEN: USXXAM
DT   Patent
LA   English
IC   ICM  G01N033-53
     ICS  C07K017-00; A61K038-00
INCL 435007100; 530350000; 530300000
CC   7-2 (Enzymes)
     Section cross-reference(s): 3, 14
FAN.CNT 8
     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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PI   US 6699671            B1    20040302    US 1999-416901         19991013 <--
     WO 2000017369         A2    20000330    WO 1999-US20881        19990923 <--
     WO 2000017369         A3    20001123
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             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
             MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
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             BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CN 1502692            A     20040609    CN 2003-10119663       19990923 <--
     CN 1502696            A     20040609    CN 2003-10119664       19990923 <--
     US 6420534            B1    20020716    US 2000-548372         20000412 <--
     US 6440698            B1    20020827    US 2000-548367         20000412 <--
     US 2003104365         A1    20030605    US 2000-548366         20000412 <--
     US 6797487            B2    20040928
     US 6706485            B1    20040316    US 2000-548376         20000412 <--
     US 6737510            B1    20040518    US 2000-548373         20000412 <--
     US 6825023            B1    20041130    US 2000-548368         20000412 <--
     US 6867018            B1    20050315    US 2000-548365         20000412 <--
     US 6500667            B1    20021231    US 2000-551853         20000418 <--
     CA 2397786            AA    20010405    CA 2000-2397786        20000922 <--
     WO 2001023533         A2    20010405    WO 2000-US26080        20000922 <--
     WO 2001023533         A3    20020510
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             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 2000076071         A5    20010430    AU 2000-76071          20000922 <--
     AU 782312             B2    20050721
     GB 2357767            A1    20010704    GB 2000-23315          20000922 <--
     GB 2357767            B2    20020821
     GB 2367060            A1    20020327    GB 2001-25934          20000922 <--
     GB 2367060            B2    20030604
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     EP 1224297          A2    20020724    EP 2000-965338          20000922 <--
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     EP 1249498          A2    20021016    EP 2002-15537           20000922 <--
     EP 1249498          A3    20040922
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            IE, SI, LT, LV, FI, RO, MK, CY, AL
     NZ 517297           A     20040430    NZ 2000-517297          20000922 <--
     US 6844148          B1    20050118    US 2000-668314          20000922 <--
     US 2001016324       A1    20010823    US 2001-794927          20010227 <--
     US 6727074          B2    20040427
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     US 6913918          B2    20050705
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        W:  US
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     US 2004048303       A1    20040311    US 2003-652830          20030829 <--
     US 2004166507       A1    20040826    US 2003-652045          20030829 <--
     US 2004234976       A1    20041125    US 2003-476935          20031106 <--
     US 2005196398       A1    20050908    US 2004-817979          20040405 <--
PRAI US 1998-101594P     P     19980924  <--
     US 1999-155493P     P     19990923  <--
     US 1999-404133      B2    19990923  <--
     WO 1999-US20881     A2    19990923  <--
     CN 1999-811202      A     19990923  <--
     GB 2000-23315       A3    19990923  <--
     US 1999-416901      A3    19991013  <--
     US 1999-169232P     P     19991206  <--
     EP 2000-965338      A3    20000922  <--
     US 2000-668314      A1    20000922  <--
     WO 2000-US26080     W     20000922  <--
     WO 2001-IB798       W     20010509
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CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 US 6699671       ICM    G01N033-53
                  ICS    C07K017-00; A61K038-00
                  INCL   435007100; 530350000; 530300000
 US 6699671       NCL    435/007.100; 530/300.000; 530/350.000
                  ECLA   C07K014/47A3; C12N009/64F2C23; C12Q001/37          <--
 WO 2000017369    ECLA   C07K014/47A3; C12N009/64F2C23                     <--
 US 6420534       NCL    435/226.000; 435/023.000; 435/024.000; 435/069.100;
                         530/350.000
                  ECLA   C07K014/47A3; C12N009/64F2C23; C12Q001/37          <--
 US 6440698       NCL    435/069.100; 435/252.300; 435/320.100; 435/325.000;
                         536/023.100
                  ECLA   C07K014/47A3; C12N009/64F2C23; C12Q001/37          <--
 US 2003104365    NCL    435/006.000
                  ECLA   C07K014/47A3; C12N009/64F2C23; C12Q001/37          <--
 US 6706485       NCL    435/007.100; 435/069.100; 435/183.000; 435/195.000;
                         435/212.000; 435/320.100; 530/300.000; 530/350.000;
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		536/023.100; 536/023.400; 536/023.500
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 6737510	NCL	530/350.000; 435/219.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 6825023	NCL	435/226.000; 435/183.000; 530/300.000; 530/324.000; 530/350.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 6867018	NCL	435/069.100; 435/252.300; 435/320.100; 435/325.000; 530/300.000; 530/350.000; 536/023.100
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 6500667	NCL	435/375.000; 514/044.000; 536/023.100; 536/024.100; 536/024.500
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
WO 2001023533	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
GB 2357767	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
GB 2367060	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
EP 1249498	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 6844148	NCL	435/004.000; 435/325.000; 530/350.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2001016324	NCL	435/007.100
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US 2001021391	NCL	424/450.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2002037315	NCL	424/450.000
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US 2002064819	NCL	435/069.100
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2001018208	NCL	435/325.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2002081634	NCL	435/007.210
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
WO 2001049097	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
WO 2001049098	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
WO 2001050829	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2005080232	NCL	530/350.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2004043408	NCL	435/006.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2004048303	NCL	435/006.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2004166507	NCL	435/006.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2004234976	NCL	435/006.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--
US 2005196398	NCL	424/146.100; 435/006.000; 435/069.100; 435/226.000; 435/320.100; 435/325.000; 536/023.200
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37 <--

AB The present invention provides protein and cDNA sequences of a novel human β -**secretase**. The present invention also provides the enzyme and enzymic procedures for cleaving the β **secretase** cleavage site of the APP protein. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease.

ST sequence human secretase screening drug Alzheimer disease

IT Protein motifs
(DTG, DSG; protein and cDNA sequences of novel human β - **secretase** and use in screening drugs for treating Alzheimer's disease)

IT **Alzheimer's disease**
Drug screening
Human
Molecular cloning
Protein sequences
cDNA sequences

(protein and cDNA sequences of novel human β - **secretase** and use in screening drugs for treating Alzheimer's disease)

IT **Amyloid precursor proteins**
RL: **BSU (Biological study, unclassified)**; RCT (Reactant); **BIOL (Biological study)**; RACT (Reactant or reagent)
(protein and cDNA sequences of novel human β - **secretase** and use in screening drugs for treating Alzheimer's disease)

IT **Amyloid**
RL: **BPN (Biosynthetic preparation)**; **BIOL (Biological study)**; PREP (Preparation)
(β-; protein and cDNA sequences of novel human β - **secretase** and use in screening drugs for treating Alzheimer's disease)

IT **666867-40-9DP**, β **-Secretase** (human), subfragments are claimed
RL: **BPN (Biosynthetic preparation)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; PREP (Preparation)
(amino acid sequence; protein and cDNA sequences of novel human β **-secretase** and use in screening drugs for treating Alzheimer's disease)

IT **666867-39-6**, DNA (human β **-secretase** cDNA plus flanks)
RL: **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**
(nucleotide sequence; protein and cDNA sequences of novel human β **-secretase** and use in screening drugs for treating Alzheimer's disease)

IT **158736-49-3P**, Proteinase asp2
RL: **BPN (Biosynthetic preparation)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; PREP (Preparation)
(protein and cDNA sequences of novel human β - **secretase** and use in screening drugs for treating Alzheimer's disease)

IT 666869-29-0, 1: PN: US6699671 SEQID: 1 unclaimed DNA 666869-31-4, 3: PN: US6699671 SEQID: 3 unclaimed DNA 666869-33-6, 7: PN: US6699671 SEQID: 7 unclaimed DNA 666869-35-8, 9: PN: US6699671 SEQID: 9 unclaimed DNA
666869-37-0 666869-39-2 666869-41-6 666869-43-8 666869-45-0
666869-47-2 666869-49-4 666869-51-8 666869-53-0 666869-55-2
666869-57-4 666869-59-6 666869-60-9 666869-61-0 666869-62-1
666869-63-2 666869-64-3 666869-65-4 666869-66-5 666869-67-6
666869-68-7 666869-69-8 666869-70-1 666869-71-2 666869-72-3
666869-73-4 666869-75-6 666869-77-8 666869-79-0 666869-81-4
666869-83-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; protein and cDNA sequences of a novel human β **-secretase** and use in screening drugs for treating Alzheimer's disease)

IT 666869-30-3 666869-32-5 666869-34-7 666869-36-9 666869-38-1
666869-40-5 666869-42-7 666869-44-9 666869-46-1 666869-48-3
666869-50-7 666869-52-9 666869-54-1 666869-56-3 666869-58-5
666869-74-5 666869-76-7 666869-78-9 666869-80-3 666869-82-5
666869-84-7 666869-85-8
RL: PRP (Properties)
(unclaimed protein sequence; protein and cDNA sequences of a novel human β **-secretase** and use in screening drugs for treating Alzheimer's disease)

IT **186142-28-9 252256-37-4** 262364-47-6 262364-48-7
300584-89-8 302566-59-2 333322-60-4 348636-36-2 350241-65-5
350241-67-7 350241-69-9 350241-71-3
RL: PRP (Properties)
(unclaimed sequence; protein and cDNA sequences of a novel human β **-secretase** and use in screening drugs for

treating Alzheimer's disease)
RE.CNT 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abraham; US 5849560 A 1998 HCAPLUS
(2) Anderson; US 5942400 A 1999 HCAPLUS
(3) Anon; WO 9631122 1996 HCAPLUS
(4) Anon; WO 9640885 1996 HCAPLUS
(5) Anon; EP 0848062 A2 1998 HCAPLUS
(6) Anon; EP 0855444 A2 1998 HCAPLUS
(7) Anon; WO 9813488 1998 HCAPLUS
(8) Anon; WO 9821589 1998 HCAPLUS
(9) Anon; WO 9826059 1998 HCAPLUS
(10) Anon; WO 9931236 1999 HCAPLUS
(11) Anon; WO 9934004 1999 HCAPLUS
(12) Anon; WO 9946281 1999 HCAPLUS
(13) Anon; WO 9964587 1999 HCAPLUS
(14) Anon; WO 0023576 2000 HCAPLUS
(15) Anon; WO 0047618 2000 HCAPLUS
(16) Anon; WO 0056871 2000
(17) Anon; WO 0058479 2000 HCAPLUS
(18) Anon; WO 0068266 2000 HCAPLUS
(19) Anon; WO 0069262 2000 HCAPLUS
(20) Anon; WO 0100663 2001 HCAPLUS
(21) Anon; WO 0100665 2001 HCAPLUS
(22) Anon; WO 0129563 2001 HCAPLUS
(23) Anon; WO 0131054 2001 HCAPLUS
(24) Anon; WO 0136600 2001 HCAPLUS
(25) Anon; WO 0138487 2001 HCAPLUS
(26) Christie; US 6358725 B1 2002 HCAPLUS
(27) Christie; US 6361975 B1 2002 HCAPLUS
(28) Chrysler; US 5744346 A 1998 HCAPLUS
(29) Chrysler; US 6221645 B1 2001 HCAPLUS
(30) Chyung; Journal of Cell Biology 1997, V138, P671 HCAPLUS
(31) Dixon; US 5733768 A 1998 HCAPLUS
(32) Dovey; US 5424205 A 1995 HCAPLUS
(33) Elan; www.elancorp.com 2000
(34) Evin; Int J Exp Clin Invest 1994, V1, P263 HCAPLUS
(35) Gurney; U S patent application Ser No 09/548,365 2000
(36) Gurney; U S patent application Ser No 09/548,366 2000
(37) Gurney; U S patent application Ser No 09/548,368 2000
(38) Gurney; U S patent application Ser No 09/548,369 2000
(39) Gurney; U S patent application Ser No 09/548,370 2000
(40) Gurney; U S patent application Ser No 09/548,373 2000
(41) Gurney; U S patent application Ser No 09/548,376 2000
(42) Gurney; U S patent application Ser No 09/794,743 2001
(43) Gurney; U S patent application Ser No 09/794,748 2001
(44) Gurney; U S patent application Ser No 09/794,925 2001
(45) Gurney; U S patent application Ser No 09/794,927 2001
(46) Gurney; U S patent application Ser No 09/795,847 2001
(47) Gurney; U S patent application Ser No 09/806,194 2001
(48) Gurney; U S patent application Ser No 09/869,414 2001
(49) Haass; Journal of Biochemistry 1993, V268, P3021 HCAPLUS
(50) Haass; Nature 1992, V359, P322 HCAPLUS
(51) Haass; Nature Medicine 1995, V12, P1291
(52) Hardy; US 5877015 A 1999 HCAPLUS
(53) Hirosawa; DNA Res 1999, V6(5), P329 HCAPLUS
(54) Hook; US 6245884 B1 2001 HCAPLUS
(55) Hook; US 6313268 B1 2001 HCAPLUS
(56) Hussain; Molecular and Cellular Neuroscience 1999, V14, P419 HCAPLUS
(57) Kang; Nature 1987, V325, P733 HCAPLUS
(58) Kitaguchi; Nature 1988, V331, P530 HCAPLUS
(59) Knops; Journal of Biological Chemistry 1995, V270, P2419 HCAPLUS
(60) Koo; Journal of Biological Chemistry 1994, V269, P17386 HCAPLUS
(61) McLonlogue; US 6245964 B1 2001 HCAPLUS
(62) Mullan; US 5455169 A 1995 HCAPLUS
(63) Mullan; US 5795963 A 1998 HCAPLUS

(64) Mullan; Nature Genetics 1992, V1, P345 HCAPLUS
(65) Ponte; Nature 1988, V331, P525 HCAPLUS
(66) Powell; US 6025180 A 2000 HCAPLUS
(67) Powell; US 6162630 A 2000 HCAPLUS
(68) Powell; US 6319689 B1 2001 HCAPLUS
(69) Schenk; US 5593846 A 1997 HCAPLUS
(70) Schenk; US 5837672 A 1998 HCAPLUS
(71) Schlossmacher; US 5766846 A 1998 HCAPLUS
(72) Seubert; Nature 1993, V361, P260 HCAPLUS
(73) Singh; US 6211428 B1 2001 HCAPLUS
(74) Sinha; Nature 1999, V402, P537 HCAPLUS
(75) Suzuki; US 5750349 A 1998 HCAPLUS
(76) Szecsi; Scand J Clin Lab Invest 1992, V52(suppl 210), P5
(77) Tanzi; Nature 1988, V331, P528 HCAPLUS
(78) Vasser; Science 1999, V286(5440), P735
(79) Yan; Nature 1999, V402, P533 HCAPLUS
(80) Zhao; Journal of Biological Chemistry 1996, V271, P31407 HCAPLUS

L43 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:473269** HCAPLUS
DN 139:47180
ED Entered STN: 20 Jun 2003
TI Treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compounds that decrease membrane depolarization or calcium influx caused by aggregated β-amyloid
IN Ingram, Vernon M.; Blanchard, Barbara J.; Stockwell, Brent R.
PA USA
SO U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U.S. Ser. No. 706,574.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-4035
INCL 514417000
CC 1-11 (Pharmacology)
Section cross-reference(s): 14
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003114510	A1	20030619	US 2002-51663	20020118 <--
	US 6942963	B1	20050913	US 2000-706574	20001103 <--
	US 2003105152	A1	20030605	US 2002-143534	20020510 <--
	WO 2003068147	A2	20030821	WO 2003-US1672	20030121
	WO 2003068147	A3	20040318		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1474126	A2	20041110	EP 2003-707454	20030121
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2000-706574	A2	20001103 <--		
	US 1997-35847P	P	19970110 <--		
	US 1997-960188	B1	19971029 <--		
	US 1998-5215	A2	19980109 <--		
	US 2002-51663	A2	20020118		
	US 2002-143534	A	20020510		
	WO 2003-US1672	W	20030121		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES

US 2003114510	ICM	A61K031-4035
	INCL	514417000
US 2003114510	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
US 6942963	NCL	435/003.000; 435/808.000; 436/063.000; 436/164.000; 436/172.000; 436/182.000; 436/800.000; 436/805.000
	ECLA	A61K038/08; C07K001/04C; C07K007/06A; G01N033/68V2 <--
US 2003105152	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
WO 2003068147	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/4035; A61K031/475; A61K031/485; A61K031/55; G01N033/68V2

AB The invention involves identification of a mechanism of β-amyloid peptide cytotoxicity, which enables treatment of conditions caused by β-amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can reduce the neurotoxic effects of such aggregates. Methods for treating conditions resulting from neurotoxic β-amyloid peptide aggregates, such as Alzheimer's disease and pharmaceutical prepns. are provided. Also provided are methods for selecting addnl. compds. which can reduce the neurotoxic effects of β-amyloid aggregates. Specifically claimed is a method for treating Alzheimer's disease using a compound that decreases membrane depolarization of neuronal cells or decreases the calcium influx caused by aggregated β-amyloid (Aβ) protein degradation products,. The compds. used in treatment are tyrosine kinase inhibitors, chloride channel antagonists, dopamine receptor agonists, and α2-adrenergic receptor antagonists. These compds. can be used in combination with β-amyloid vaccine.

ST beta amyloid aggregate neurotoxicity treatment membrane depolarization inhibitor; Alzheimers disease treatment membrane depolarization inhibitor; calcium influx inhibitor beta amyloid aggregate neurotoxicity treatment

IT Membrane potential
(biol.; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Glutamate antagonists
(mGluR1; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Fluorescent substances
(potentiometric, for drug screening assay; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Chloride channel blockers
(treatment composition containing; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT **Anti-Alzheimer's agents**
(treatment of; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT **Alzheimer's disease**
Biological transport
Cell membrane
Dopamine agonists
Drug screening
Human
Nerve
Nervous system agents
Neurotoxicity
(treatments for conditions caused by neurotoxic β-amyloid peptide

aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Peptides, biological studies
RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Adrenoceptor antagonists
(α2-, treatment composition containing; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT **Amyloid**
RL: **ADV (Adverse effect, including toxicity); BIOL (Biological study)**
(β-; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Vaccines
(β-amyloid, along with agents inhibiting neuronal membrane depolarization; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT 70363-83-6, Bis(1,3-dibutylbarbituric acid) trimethine oxonol
RL: **ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study)**; USES (Uses)
(as potentiometric agent for drug screening; treatment for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β-amyloid)

IT **158736-49-3, β -Secretase** 338454-52-7, γ-Secretase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(combined treatment with a secretase inhibitor; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT 79079-06-4, EGF receptor tyrosine kinase 80449-02-1, Tyrosine kinase 152787-58-1, TrkA receptor tyrosine kinase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(inhibitors, treatment composition containing; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT 7440-70-2, Calcium, biological studies
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(transport; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT 51-61-6, Dopamine, biological studies 55-10-7, Vanillyl-mandelic acid 131-03-3, Rauwolscine 911-45-5, Clomiphene 1845-11-0, Nafoxidine 71636-61-8, SKF81297 118409-60-2, Tyrphostin 47 145915-58-8, 4,5-Dianilinophthalimide 148741-30-4, Tyrphostin AG 879 150145-89-4 198419-91-9, LY367385
RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(treatment for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β-amyloid)

IT 69-65-8, D-Mannitol 83-67-0, Theobromine 111-58-0, N-Oleoylethanolamine 130-61-0, Thioridazine Hydrochloride 302-27-2, Aconitine 312-84-5, D-Serine 569-57-3, Chlorotrianisene 646-25-3, 1,10-Diaminodecane 1847-63-8, Nafoxidine hydrochloride 2315-02-8, Oxymetazoline Hydrochloride 2792-66-7, α-Methyl-DL-aspartic acid

3724-89-8 5302-45-4 6211-32-1, Rauwolscine hydrochloride 6620-60-6, Proglumide 9087-70-1, Aprotinin 13311-84-7, Flutamide 13434-13-4, Actinonin 24280-93-1, Mycophenolic acid 33507-63-0, Substance P (peptide) 34183-22-7, Propafenone Hydrochloride 37686-84-3 39740-82-4 42200-33-9, Nadolol 54965-24-1, Tamoxifen citrate 66104-23-2, Pergolide methanesulfonate 73590-58-6, Omeprazole 76824-35-6, Famotidine 78739-01-2, D-(-)-2-Amino-4-Phosphonobutyric acid 97752-20-0 130506-22-8, 6-Nitroso-1,2-benzopyrone
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT 543805-01-2 543805-02-3
RL: PRP (Properties)
(unclaimed protein sequence; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β-amyloid)

IT 131602-53-4
RL: PRP (Properties)
(unclaimed sequence; treatments for conditions caused by neurotoxic β-amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β-amyloid)

L43 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:435317** HCAPLUS
DN 139:30831
ED Entered STN: 06 Jun 2003
TI Treatments for neurotoxicity in Alzheimer's disease
IN Ingram, Vernon M.; Blanchard, Barbara J.; Stockwell, Brent R.
PA USA
SO U.S. Pat. Appl. Publ., 34 pp., Cont.-in-part of U.S. Ser. No. 51,663.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-4035
ICS C12Q001-00
INCL 514417000; 435004000
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003105152	A1	20030605	US 2002-143534	20020510 <--
	US 6942963	B1	20050913	US 2000-706574	20001103 <--
	US 2003114510	A1	20030619	US 2002-51663	20020118 <--
	WO 2003068147	A2	20030821	WO 2003-US1672	20030121
	WO 2003068147	A3	20040318		
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	EP 1474126	A2	20041110	EP 2003-707454	20030121
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2000-706574	A2	20001103 <--		
	US 2002-51663	A2	20020118		
	US 1997-35847P	P	19970110 <--		
	US 1997-960188	B1	19971029 <--		

US 1998-5215 A2 19980109 <--
US 2002-143534 A 20020510
WO 2003-US1672 W 20030121

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003105152	ICM	A61K031-4035
	ICS	C12Q001-00
	INCL	514417000; 435004000
US 2003105152	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
US 6942963	NCL	435/003.000; 435/808.000; 436/063.000; 436/164.000; 436/172.000; 436/182.000; 436/800.000; 436/805.000
	ECLA	A61K038/08; C07K001/04C; C07K007/06A; G01N033/68V2 <--
US 2003114510	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
WO 2003068147	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/4035; A61K031/475; A61K031/485; A61K031/55; G01N033/68V2

AB The invention involves identification of a mechanism of β-amyloid peptide cytotoxicity, which enables treatment of conditions caused by β-amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can reduce the neurotoxic effects of such aggregates. Methods for treating conditions resulting from neurotoxic β-amyloid peptide aggregates, such as Alzheimer's disease and pharmaceutical prepns. are provided. Also provided are methods for selecting addnl. compds. which can reduce the neurotoxic effects of β-amyloid aggregates. Aβ1-42 aggregates increased neuronal cell depolarization in rat PC12 and human NT neuronal cells. A random library of 1540 biol. active compds. was screened against undifferentiated PC12 cells pretreated with Aβ1-42 peptide. The most effective elimination of depolarization was achieved with two tyrosine kinase inhibitors, DAPH1 (4,5-dianilinophthalimide, EGF-receptor specific) and Tyrphostin AG879 (TrkA specific), and also nafoxidine (antiestrogen receptor, chloride channel antagonist). These were active in low micromolar concentration

ST neurotoxicity beta amyloid Alzheimer disease treatment; neuron membrane depolarization beta amyloid aggregate; tyrosine kinase inhibitor Alzheimer treatment; nafoxidine Alzheimer treatment neuron membrane stabilization

IT Vaccines
(Aβ, along with agents inhibiting neuronal membrane depolarization; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Animal cell line
(PC12; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Membrane potential
(biol.; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Cell membrane
(compds. decreasing β-amyloid aggregate-caused depolarization of neuronal cell; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT **Drug screening**
Human
Nerve
Neurotoxicity
(compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT High throughput screening
(drug; compns. and methods for treatment of β-amyloid aggregate

neurotoxicity in Alzheimer's disease and for drug screening)
IT **Drug screening**
(high throughput; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Glutamate antagonists
(mGluR1, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Glutamate receptors
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(metabotropic, mGluR1, antagonists, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Nerve
(neuron; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Fluorescent substances
(potentiometric; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Chemical compounds
(screening of small; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Combinatorial library
(screening of; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Peptides, biological studies
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(screening of; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Chloride channel blockers
Dopamine agonists
(treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT **Alzheimer's disease**
(treatment of; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT Adrenoceptor antagonists
(α2-, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT **Amyloid**
RL: **ADV (Adverse effect, including toxicity)**; **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(β-; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT 911-45-5, Clomiphene 1845-11-0, Nafoxidine
RL: **BSU (Biological study, unclassified)**; CST (Combinatorial study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; CMBI (Combinatorial study); USES (Uses)
(as chloride channel antagonist, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
IT 55-10-7, Vanillyl-mandelic acid 71636-61-8, SKF81297
RL: **BSU (Biological study, unclassified)**; CST (Combinatorial study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; CMBI (Combinatorial study); USES (Uses)
(as dopamine receptor agonist, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in

Alzheimer's disease and for drug screening)

IT 51-61-6, Dopamine, biological studies
RL: **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(as dopamine receptor agonist, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 150145-89-4 168560-79-0, AIDA 198419-91-9, LY367385
RL: **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(as mGluR1 antagonist, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 70363-83-6, Bis(1,3-dibutylbarbituric acid) trimethine oxonol
RL: **ARG (Analytical reagent use)**; **BSU (Biological study, unclassified)**; **ANST (Analytical study)**; **BIOL (Biological study)**; USES (Uses)
(as potentiometric agent for drug screening; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 446-72-0, Genistein 70563-58-5, Herbimycin A 71897-07-9, Tyrphostin AG 1295 125697-92-9, Lavendustin A 153436-53-4, Tyrphostin AG 1478
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(as tyrosine kinase inhibitor inactive in assay for reduction of membrane depolarization; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 145915-58-8, 4,5-Dianilinophthalimide
RL: **BSU (Biological study, unclassified)**; CST (Combinatorial study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; CMBI (Combinatorial study); USES (Uses)
(as tyrosine kinase inhibitor, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 118409-60-2, Tyrphostin 47 148741-30-4, Tyrphostin AG 879
RL: **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(as tyrosine kinase inhibitor, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 131-03-3, Rauwolscine
RL: **BSU (Biological study, unclassified)**; CST (Combinatorial study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; CMBI (Combinatorial study); USES (Uses)
(as α2-adrenergic receptor antagonist, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 338454-52-7, γ-Secretase
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 69-65-8, D-Mannitol 83-67-0, Theobromine 111-58-0, N-Oleoylethanolamine 130-61-0, Thioridazine Hydrochloride 302-27-2, Aconitine 312-84-5, D-Serine 569-57-3, Chlorotrianisene 646-25-3, 1,10-Diaminodecane 1847-63-8, Nafoxidine hydrochloride 2315-02-8, Oxymetazoline Hydrochloride 2792-66-7, α-Methyl-DL-aspartic acid 3724-89-8 5302-45-4 6211-32-1, Rauwolscine hydrochloride 6620-60-6, Proglumide 9087-70-1, Aprotinin 13311-84-7, Flutamide 13434-13-4, Actinonin 24280-93-1, Mycophenolic acid 34183-22-7, Propafenone Hydrochloride 37686-84-3 39740-82-4 42200-33-9, Nadolol

54965-24-1, Tamoxifen citrate 66104-23-2, Pergolide methanesulfonate
73590-58-6, Omeprazole 76824-35-6, Famotidine 78739-01-2,
D-(-)-2-Amino-4-Phosphonobutyric acid 97752-20-0 130506-22-8,
6-Nitroso-1,2-benzopyrone
RL: **BSU (Biological study, unclassified)**; CST (Combinatorial study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; CMBI (Combinatorial study); USES (Uses)
(compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 33507-63-0, Substance P (peptide)
RL: **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 7440-70-2, Calcium, biological studies
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(decreasing aggregated β-amyloid-caused neuronal cell influx of; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT **158736-49-3**, β **-Secretase**
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(inhibitor, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 79079-06-4, EGF receptor tyrosine kinase 80449-02-1, Tyrosine kinase
152787-58-1, TrkA receptor tyrosine kinase
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(inhibitors, treatment composition containing; compns. and methods for treatment of β-amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT 539902-04-0 539902-05-1
RL: PRP (Properties)
(unclaimed protein sequence; treatments for neurotoxicity in Alzheimer's disease)

IT 131602-53-4
RL: PRP (Properties)
(unclaimed sequence; treatments for neurotoxicity in Alzheimer's disease)

L43 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:615647** HCAPLUS
DN 137:150257
ED Entered STN: 16 Aug 2002
TI Method of treating amyloid $G(B) precursor protein disorder
IN Friedhoff, Lawrence; Buxbaum, Joseph; Cullen, Edward I.
PA Andrx Corporation, USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002062824	A2	20020815	WO 2002-US3256	20020205
	WO 2002062824	A3	20021121		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

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            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
            RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
            UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
            CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
            BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
    US 2002107173        A1    20020808    US 2002-67593          20020205 <--
    CA 2437480           AA    20020815    CA 2002-2437480        20020205
    EP 1366061           A2    20031203    EP 2002-718903         20020205
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
    US 2005215621        A1    20050929    US 2005-72863          20050304 <--
PRAI US 2001-265886P     P     20010205
    US 1999-163608P      P     19991104  <--
    US 2000-219435P      P     20000720  <--
    US 2000-223987P      P     20000809  <--
    US 2002-67593        A1    20020205
    WO 2002-US3256       W     20020205
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2002062824    ICM    C07K
 WO 2002062824    ECLA   A61K031/00; A61K031/192; A61K031/22; A61K031/366;
                         A61K031/40; A61K031/401; G01N033/68V2
 US 2002107173    NCL    514/001.000
                  ECLA   A61K031/00; A61K031/192; A61K031/22; A61K031/366;
                         A61K031/40; A61K031/401; G01N033/68V2              <--
 CA 2437480       ECLA   A61K031/00; A61K031/192; A61K031/22; A61K031/366;
                         A61K031/40; A61K031/401; G01N033/68V2
 EP 1366061       ECLA   A61K031/00; A61K031/192; A61K031/22; A61K031/366;
                         A61K031/40; A61K031/401; G01N033/68V2
 US 2005215621    NCL    514/423.000; 514/460.000; 514/548.000; 435/007.100;
                         435/007.920
                  ECLA   A61K031/00; A61K031/192; A61K031/22; A61K031/366;
                         A61K031/40; A61K031/401; G01N033/68V2              <--
AB   Methods for the treatment and prevention of APP processing disorders such
     as Alzheimer's disease and Down's Syndrome which are based on the
     administration of an effective amount of a HMG-CoA reductase inhibitor to a
     mammal are disclosed.  Addnl., methods for the treatment and prevention of
     APP processing disorders such as Alzheimer's disease and Down's Syndrome
     which are based on the reduction of cellular cholesterol in a mammal are
     disclosed.  These methods reduce the amount of Aβ peptides or decrease
     the formation of Aβ peptides or increase the clearance of Aβ
     peptides in a mammal suffering from Alzheimer's disease and Down's
     Syndrome.
ST   amyloid precursor protein disorder HMG CoA reductase inhibitor
IT   Immunoassay
        (agglutination test; method of treating amyloid precursor protein
        disorders using HMG-CoA reductase inhibitors and other agents in
        relation to determination of β-amyloid peptides in body fluids)
IT   Bioassay
        (complement fixation assay; method of treating amyloid precursor
        protein disorders using HMG-CoA reductase inhibitors and other agents
        in relation to determination of β-amyloid peptides in body fluids)
IT   Immunoassay
        (enzyme-linked immunosorbent assay; method of treating amyloid
        precursor protein disorders using HMG-CoA reductase inhibitors and
        other agents in relation to determination of β-amyloid peptides in body
        fluids)
IT   Immunoassay
        (fluorescence; method of treating amyloid precursor protein disorders
        using HMG-CoA reductase inhibitors and other agents in relation to
        determination of β-amyloid peptides in body fluids)
IT   Immunoassay
        (immunoblotting; method of treating amyloid precursor protein disorders
        using HMG-CoA reductase inhibitors and other agents in relation to
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determination of β-amyloid peptides in body fluids)
IT Immunoassay
(immunodiffusion, gel diffusion; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Immunoassay
Immunoassay
(immunodiffusion; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Immunoassay
(immunoelectrophoresis; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Immunoassay
(immunoradiometric assay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Buffers
(in β-amyloid peptide assays; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT **Alzheimer's disease**
Anti-Alzheimer's agents
Down's syndrome
Drug delivery systems
Drug screening
Human
Hypolipemic agents
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT **Amyloid precursor proteins**
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT Antibodies and Immunoglobulins
RL: **ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)**; USES (Uses)
(monoclonal, to β-amyloid peptides, capture and detection; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Anti-inflammatory agents
(nonsteroidal; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT Drug delivery systems
(oral, controlled-release; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT Antibodies and Immunoglobulins
RL: **ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)**; USES (Uses)
(precipitins, to β-amyloid peptides, immunoassay with; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)

IT Immunoassay
(protein A; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Immunoassay
(radioimmunoassay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Immunoassay
(sandwich; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Antibodies and Immunoglobulins
RL: **ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)**; USES (Uses)
(to β-amyloid peptides, capture and detection; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT **Amyloid**
RL: **ADV (Adverse effect, including toxicity); ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)**
(β-, lowering of; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT Blood plasma
Blood serum
Brain
Cerebrospinal fluid
(β-amyloid peptides decrease in; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT Blood analysis
Body fluid
(β-amyloid peptides determination in; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β-amyloid peptides in body fluids)
IT 9028-35-7, HMG-CoA reductase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(HMG-CoA reductase, inhibitors; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT 75225-51-3, Lovastatin acid
RL: **BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT 75330-75-5, Lovastatin
RL: **PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)
IT 73573-88-3, Mevastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin

93957-54-1, Fluvastatin 134523-00-5, Atorvastatin 143201-11-0, Rivastatin
RL: **PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)

IT **158736-49-3, β -Secretase** 338454-52-7, γ-Secretase 338455-07-5, α-Secretase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(modifiers; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β-amyloid peptides in body fluids)

L43 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:518834** HCAPLUS
DN 137:59522
ED Entered STN: 12 Jul 2002
TI Crystal structure of beta-site APP-cleaving enzyme (BACE) and uses thereof
IN Choppa, Rajiv; Svenson, Kristine; Annis, Bethany; Akopian, Tatos N.; Bard, Jonathan; Stahl, Mark Lloyd; Somers, William S.
PA American Home Products Corporation, USA
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
IC G01N033-483
CC 7-5 (Enzymes)
Section cross-reference(s): 1, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002025276	A1	20020328	WO 2001-US29387	20010919 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002055459	A1	20020509	US 2001-955737	20010919 <--
PRAI US 2000-234576P	P	20000922 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002025276	IC	G01N033-483
WO 2002025276	ECLA	C07K014/47A3; C12N009/64F <--
US 2002055459	NCL	514/001.000
	ECLA	C07K014/47A3; C12N009/64F <--

AB This invention is directed to the three dimensional crystal structure of Beta-site APP Cleaving Enzyme (BACE), and to the use of this structure in rational drug design methods to identify agents that may interact with active sites of BACE. Such agents may represent new therapeutics in the treatment and/or prevention of Alzheimer's Disease. The amino acid sequence of the aspartic proteinase BACE is recorded in SwissProt accession number P56817. BACE is the β **-secretase** that cleaves β-amyloid precursor protein (APP) at residue 671. An APP-inhibitor peptide has the sequence SER-GLU-VAL-ASN-Sta-VAL-ALA-GLU-PHE, where Sta is the rare amino acid S-statine.
ST **beta secretase** BACE crystal structure drug screening

Alzheimer
IT **Amyloid precursor proteins**
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(cleavage of; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **Alzheimer's disease**
Anti-Alzheimer's agents
Crystal structure
Drug screening
Human
Molecular cloning
Molecular structure
X-ray diffractometry
(crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT Crystallography
(x-ray; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **439546-25-5**, **β -secretase** (human gene BACE)
RL: **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**
(amino acid sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **158736-49-3**, β-Site APP cleaving enzyme
RL: **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**
(crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **439085-08-2**
RL: **PAC (Pharmacological activity)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **392103-88-7**, GenBank AF190725
RL: **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**
(nucleotide sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)
IT **439549-44-7** **439549-87-8**
RL: PRP (Properties)
(unclaimed sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) and uses thereof)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bailey; Biochem J 1993, V289, P363 HCAPLUS
(2) Hong, L; Science 2000, V290(5489), P150 HCAPLUS
(3) Hynes; Biochemistry 1990, V29, P10018 HCAPLUS
(4) Kohno; Biochemistry 1996, V35, P16094 HCAPLUS
(5) Marcinkeviciene, J; The Journal of Biological Chemistry 2001, V276(26), P23790 HCAPLUS
(6) Rossjohn; Nature Structural Biology 1999, V6(4), P327 HCAPLUS
(7) Sauder, M; J Mol Biol 2000, V300(2), P241
(8) Scheidig; The Protein Society 1997, V6, P1806 HCAPLUS
(9) Vassar; Science 1999, V286, P735 HCAPLUS
(10) Zhang, Z; The EMBO Journal 1997, V16(20), P6141 HCAPLUS

L43 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:107514** HCAPLUS
DN 136:163293
ED Entered STN: 10 Feb 2002
TI BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or

treatment of neurodegenerative disorders
IN Seidah, Nabil G.; Chretien, Michel; Cromlish, James A.
PA Institut De Recherche Cliniques De Montreal (IRCM), Can.
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N009-00
CC 7-2 (Enzymes)
Section cross-reference(s): 1, 13, 14
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002010354	A2	20020207	WO 2001-CA1118	20010801 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2313828	AA	20020201	CA 2000-2313828	20000801 <--
CA 2417873	AA	20020207	CA 2001-2417873	20010801 <--
US 2004180417	A1	20040916	US 2004-343389	20040405 <--
PRAI CA 2000-2313828	A	20000801 <--		
WO 2001-CA1118	W	20010801		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002010354	ICM	C12N009-00
WO 2002010354	ECLA	C07K014/47A3; C12N009/64F <--
CA 2313828	ECLA	C07K014/47A3; C12N009/64F <--
CA 2417873	ECLA	C07K014/47A3; C12N009/64F <--
US 2004180417	NCL	435/184.000
	ECLA	C07K014/47A3; C12N009/64F <--

AB The present invention relates to β -**secretase** referred to as the beta-site APP-cleaving enzyme (BACE, Asp2, **memapsin 2**). More specifically, the present invention concerns a novel Asp-ase that processes BACE, referred to as BACE secretase/sheddase, and the use of this enzyme in the diagnosis, prevention or treatment of neurodegenerative disorders, such as Alzheimer's Disease. The present invention further comprises the use of BACE secretase/sheddase in a screening assay for the identification of agents capable of modifying its activity (modulating agents) as well as the use of BACE secretase/sheddase in a kit. A novel Asp-ase activity, referred to as BACE secretase/sheddase, has been found to cleave the ectodomain of BACE after Asp379 (SQDD↓) and Asp407 (VVFD↓), and likely after Asp451 (PQTD↓). The cleavage of BACE by BACE secretase/sheddase renders BACE soluble which in turns appears to enhance the generation of the amyloidogenic peptide Aβ, which has been implicated as a major factor in the etiol. of Alzheimer's Disease. Since truncation of BACE leads to increased Aβ production, BACE secretase/sheddase is an attractive target to modulate for medicinal and research purposes.
ST BACE secretase sheddase Asp ase neurodegenerative disorder diagnosis therapy
IT **Alzheimer's disease**
Drug screening
High throughput screening
Susceptibility (genetic)
Test kits
(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)
IT Antibodies and Immunoglobulins

Antisense oligonucleotides
Ribozymes
RL: **THU (Therapeutic use); BIOL (Biological study);**
USES (Uses)
(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Cerebrospinal fluid
Platelet (blood)
(anal. of, for diagnosis; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Nervous system, disease
(degeneration; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Peptides, biological studies
RL: **THU (Therapeutic use); BIOL (Biological study);**
USES (Uses)
(inhibitor; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Diagnosis
(mol.; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT **Amyloid precursor proteins**
RL: **ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study);** USES (Uses)
(use in screening; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT **Amyloid**
RL: **ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study);** USES (Uses)
(β-, anal. of the level of, for diagnosis; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT **396078-28-7**, BACE secretase/sheddase
RL: **ARU (Analytical role, unclassified); BSU (Biological study, unclassified);** PRP (Properties); **THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);**
USES (Uses)
(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT **158736-49-3**, β-Site APP-cleaving enzyme
RL: **BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study);** USES (Uses)
(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 397251-28-4
RL: PRP (Properties)
(Unclaimed; bACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 98849-88-8 141074-86-4 182916-29-6 252256-47-6 395183-00-3
395183-01-4 395183-02-5 395183-03-6 397251-18-2 397251-19-3
397251-20-6 397251-21-7 397251-22-8 397251-23-9 397251-24-0
397251-25-1 397251-26-2 397251-27-3 397251-29-5

RL: PRP (Properties)
(unclaimed sequence; bACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Creemers, J; THE JOURNAL OF BIOLOGICAL CHEMISTRY 2001, V276(6), P4211 HCAPLUS
(2) Duguay, S; JOURNAL OF BIOLOGICAL CHEMISTRY 1998, V273(29), P18443 HCAPLUS
(3) Ermolieff; BIOCHEMISTRY 2000, V39, P12450 HCAPLUS
(4) Haniu, M; JOURNAL OF BIOLOGICAL CHEMISTRY 2000, V275(28), P21099 HCAPLUS
(5) Lin, X; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 2000, V97(4), P1456 HCAPLUS
(6) Potter; NATURE BIOTECHNOLOGY 2000, V18, P125 HCAPLUS
(7) Schering Ag; DE 19641180 A 1998 HCAPLUS
(8) Seubert, P; NATURE 1992, V359(6393), P325 HCAPLUS
(9) Skovronsky, D; TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL 2000, V21(5), P161 HCAPLUS
(10) Turner, J; WO 9813488 A 1998 HCAPLUS
(11) Vassar, R; SCIENCE 1999, V286(5440), P735 HCAPLUS

L43 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:10812** HCAPLUS
DN 136:79718
ED Entered STN: 04 Jan 2002
TI Rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening
IN Bamdad, Cynthia C.; Bamdad, R. Shoshana
PA Minerva Biotechnologies Corporation, USA
SO PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-68
CC 1-1 (Pharmacology)
Section cross-reference(s): 14

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002001230	A2	20020103	WO 2001-US20232	20010625 <--
	WO 2002001230	A3	20030814		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2413884	AA	20020103	CA 2001-2413884	20010625 <--
	AU 2001070157	A5	20020108	AU 2001-70157	20010625 <--
	EP 1356296	A2	20031029	EP 2001-948711	20010625 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
	JP 2004526124	T2	20040826	JP 2002-506112	20010625 <--
PRAI	US 2000-602689	A	20000623	<--	
	US 2000-631818	A	20000803	<--	
	WO 2001-US20232	W	20010625		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002001230	ICM	G01N033-68
WO 2002001230	ECLA	G01N033/543M; G01N033/68V2 <--

JP 2004526124 FTERM 2G045/AA25; 2G045/CA25; 2G045/CA26; 2G045/CA30; 2G045/CB17; 2G045/CB30; 2G045/DA36; 2G045/FA11; 2G045/FA34; 2G045/FB11; 2G045/JA01; 2G054/AA06; 2G054/AA07; 2G054/AA08; 2G054/AA10; 2G054/AB02; 2G054/AB05; 2G054/CA21; 2G054/CA22; 2G054/CA23; 2G054/EA03; 2G054/EA06; 2G054/FB01; 2G054/GA03; 2G054/GA04; 2G054/GE01; 2G059/AA01; 2G059/BB12; 2G059/BB14; 2G059/DD03; 2G059/DD13; 2G059/EE01; 2G059/EE02; 2G059/EE07; 2G059/EE12; 2G059/EE13; 2G059/FF03; 2G059/HH02; 2G059/KK04; 2G059/KK06; 2G059/KK07; 4B063/QA05; 4B063/QA20; 4B063/QQ79; 4B063/QQ91; 4B063/QR16; 4B063/QR55; 4B063/QR58; 4B063/QR82; 4B063/QS12; 4B063/QS22; 4B063/QS32; 4B063/QX01 <--

AB Methods, assays, and components are described in which biol. samples can be rapidly and sensitively analyzed for the presence of species associated with neurodegenerative disease. Techniques and components are provided for diagnosis of disease, as well as for screening of candidate drugs for treatment of neurodegenerative disease. The techniques are simple, extremely sensitive, and utilize readily-available components. Binding species, capable of binding a neurodegenerative disease aggregate-forming or aggregate-forming species, are fastened to surfaces of electrodes and surfaces of particles, or provided free in solution, to bind aggregate-forming species and/or be involved in aggregation.

ST aberrant protein fibril aggregation colloid; drug screening neurodegenerative disease kit

IT Brain, disease
Prion diseases
(Creutzfeldt-Jakob; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
RL: **DGN (Diagnostic use)**; PRP (Properties); **BIOL (Biological study)**; USES (Uses)
(PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Voltammetry
(a.c.; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Spheres
(beads; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
RL: **DGN (Diagnostic use)**; PRP (Properties); **BIOL (Biological study)**; USES (Uses)
(bovine spongiform encephalopathy; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Proteins
RL: **DGN (Diagnostic use)**; PRP (Properties); **BIOL (Biological study)**; USES (Uses)
(complexes; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nervous system, disease
(degeneration; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Self-assembled monolayers
(electroactive; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Immunoassay
(enzyme-linked immunosorbent assay; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies

RL: **PAC (Pharmacological activity)**; PRP (Properties); **BIOL (Biological study)**
(inhibitors, capsase; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Carboxyl group
(ionized; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Aggregation
Alzheimer's disease
Animal
Animal cell
Blood analysis
Cerebrospinal fluid
Colloids
Diagnosis
Drug screening
Feed
Fibril
High throughput screening
Human
Immobilization, molecular or cellular
Livestock
Magnetic particles
Microtiter plates
Milk
Molecular association
Molecular recognition
Parkinson's disease
Protein sequences
Test kits
Transplant and Transplantation
UV and visible spectroscopy
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies
RL: **BSU (Biological study, unclassified)**; **PAC (Pharmacological activity)**; PRP (Properties); **BIOL (Biological study)**
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT p53 (protein)
RL: **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Metallocenes
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT DNA
RL: **DGN (Diagnostic use)**; PRP (Properties); **BIOL (Biological study)**; USES (Uses)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Peptides, biological studies
RL: **PAC (Pharmacological activity)**; PRP (Properties); **BIOL (Biological study)**
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nucleic acids
Oligonucleotides
Proteins
RL: PRP (Properties)
(rapid and sensitive detection of aberrant protein(fibril) aggregation

in neurodegenerative disease diagnosis and drug screening)

IT Antibodies and Immunoglobulins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Brain, disease
(spongiform encephalopathy, transmissible; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Sensors
(surface plasmon resonance chip; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Transferrins
RL: BSU (Biological study, unclassified); CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(τ-transferrins; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Amyloid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(β-, C-terminal fragment; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Amyloid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(β-; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 167396-02-3 286411-43-6 286411-44-7 286411-46-9 286411-47-0 286411-48-1
RL: PRP (Properties)
(Unclaimed; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 7732-18-5, Water, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 58-85-5, 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- 70-18-8, Glycine, L-γ-glutamyl-L-cysteinyl-, properties 102-54-5, Ferrocene 139-13-9, Glycine, N,N-bis(carboxymethyl)- 573-58-0, 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis4-amino-, disodium salt 2390-54-7, Benzothiazolium, 2-[4-(dimethylamino)phenyl]-3,6-dimethyl-, chloride 6066-82-6, 2,5-Pyrrolidinedione, 1-hydroxy- 9001-78-9, Phosphatase, alkaline 9013-20-1, Streptavidin 10487-90-8, Phenol, 2,2'-[(6,6'-dimethyl[1,1'-biphenyl]-2,2'-diyl)bis(nitrilomethylidyne)]bis- 64691-70-9, Pyridine, 2,2'-[1,2-ethanediylbis(thio-2,1-ethanediyl)]bis-
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 7440-57-5, Gold, properties
RL: DEV (Device component use); PRP (Properties); USES (Uses)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 78990-62-2, Calpain 158736-49-3, β-Secretase 338454-52-7, γ-Secretase
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)

(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

L43 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:780679** HCAPLUS
DN 135:327362
ED Entered STN: 26 Oct 2001
TI Nonsteroidal antiinflammatory drug (NSAID) and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for the treatment of Alzheimer's disease, and screening methods
IN Koo, Edward Hao Mang; Golde, Todd Eliot; Galasko, Douglas Roger
PA Mayo Foundation for Medical Education and Research, USA
SO PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-24; A61K031-195; A61K031-165
CC 1-11 (Pharmacology)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2001078721	A1	20011025	WO 2001-US11956	20010412	<--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	CA 2406383	AA	20011025	CA 2001-2406383	20010412	<--
	AU 2001057022	A5	20011030	AU 2001-57022	20010412	<--
	EP 1284729	A1	20030226	EP 2001-930491	20010412	<--
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	JP 2003530437	T2	20031014	JP 2001-576021	20010412	<--
	US 2002128319	A1	20020912	US 2001-12606	20011207	<--
	US 6911466	B2	20050628			
	US 2005089945	A1	20050428	US 2004-928925	20040827	<--
	US 2005186559	A1	20050825	US 2005-113789	20050425	<--
PRAI	US 2000-196617P	P	20000413	<--		
	WO 2001-US11956	W	20010412			
	US 2001-12606	A3	20011207			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001078721	ICM	A61K031-40	
	ICS	A61K031-24; A61K031-195; A61K031-165	
WO 2001078721	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
CA 2406383	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
AU 2001057022	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
EP 1284729	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
US 2002128319	NCL	514/569.000	
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
US 2005089945	NCL	435/023.000	
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2	<--
US 2005186559	NCL	435/004.000; 435/006.000; 436/086.000	
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24;	

A61K031/40; G01N033/68V2 <--

AB A method is provided for preventing, delaying, or reversing the progression of Alzheimer's disease by administering an Aβ42-lowering agent to a mammal under conditions in which levels of Aβ42 are selectively reduced, levels of Aβ38 are increased, and levels of Aβ40 are unchanged. The invention provides methods and materials for developing and identifying Aβ42-lowering agents. In addition, the invention provides methods for identifying agents that increase the risk of developing, or hasten progression of, Alzheimer's disease. The invention also provides compns. of Aβ42-lowering agents and antioxidants, Aβ42 lowering agents and non-selective secretase inhibitors, and Aβ42 lowering agents and acetylcholinesterase inhibitors. The invention further provides kits containing Aβ42-lowering agents, antioxidants, non-selective secretase inhibitors, and/or acetylcholinesterase inhibitors as well as instructions related to dose regimens for Aβ42-lowering agents, antioxidants, non-selective secretase inhibitors, and acetylcholinesterase inhibitors. The agents of the invention include nonsteroidal antiinflammatory drugs (NSAIDs) and NSAID derivs.

ST amyloid Abeta42 lowering agent Alzheimer drug; NSAID amyloid Abeta42 lowering agent Alzheimer drug; screening amyloid Abeta42 lowering agent Alzheimer drug

IT **Alzheimer's disease**
Anti-Alzheimer's agents
Drug design
Drug screening
Ginkgo biloba
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Enzymes, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Amino acids, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid precursor proteins**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PROC (Process)
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Metabolism
(catabolic; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Animal cell
(mammalian; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Anti-inflammatory agents
(nonsteroidal, and derivs.; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Antioxidants
(pharmaceutical; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT Transgene
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PROC (Process)
(transgenic animal; NSAID and NSAID derivative amyloid Aβ42

polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ34; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ36; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ37; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ38; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ39; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ40; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **Amyloid**
RL: **BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)**
(β-, Aβ42; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT 50-78-2, Aspirin 80-08-0, Dapsone 489-84-9, Guaiazulene 501-36-0, Resveratrol 642-72-8, Benzydamine 4394-00-7, Niflumic acid 13710-19-5, Tolfenamic acid 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22494-42-4, Diflunisal 27470-51-5, Suxibuzone 31842-01-0, Indoprofen 34552-84-6, Isoxicam 36322-90-4, Piroxicam 36330-85-5, Fenbufen 40828-46-4, Suprofen 41340-25-4, Etodolac 42924-53-8, Nabumetone 51803-78-2, Nimesulide 53164-05-9, Acemetacin 59804-37-4, Tenoxicam 59973-80-7, Sulindac sulfone 71125-38-7, Meloxicam 74103-06-3, Ketorolac 123653-11-2, NS-398 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 188817-13-2, SC560 209125-28-0
RL: **BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)**
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT 50-81-7, Vitamin C, biological studies 53-86-1, Indomethacin 53-86-1D, Indomethacin, derivs. 61-68-7, Mefenamic acid 64-19-7D, Acetic acid, aryl derivs., biological studies 79-09-4D, Propionic acid, aryl derivs. 458-37-7, Curcumin 530-78-9, Flufenamic acid 530-78-9D, Flufenamic acid, derivs. 644-62-2, Meclofenamic acid 644-62-2D, Meclofenamic acid, derivs. 1406-18-4, Vitamin E 1601-18-9 2878-86-6 5104-49-4,

Flurbiprofen 5104-49-4D, Flurbiprofen, derivs. 6264-33-1 15687-27-1, Ibuprofen 15687-27-1D, Ibuprofen, derivs. 22071-15-4D, Ketoprofen, derivs. 29679-58-1, Fenoprofen 29679-58-1D, Fenoprofen, derivs. 49627-27-2, Sulindac sulfide 49627-27-2D, Sulindac sulfide, derivs. 53716-49-7, Carprofen 53716-49-7D, Carprofen, derivs. 60051-81-2 63170-54-7 80590-83-6 83196-74-1 107254-86-4, NPPB 107254-86-4D, 5-Nitro-2-(3-phenylpropylamino)benzoic acid, derivs. 176174-97-3 261766-23-8 261766-24-9 261766-25-0 261766-26-1 261766-27-2 261766-28-3 261766-29-4 261766-30-7 261766-32-9 261766-35-2 261766-36-3 261766-37-4 261766-38-5 261766-39-6 261766-40-9 261766-41-0 261766-42-1 261766-43-2 288854-06-8 288854-11-5
RL: **BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study)**; USES (Uses)
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT **158736-49-3, β -Secretase** 329900-75-6, Cyclooxygenase 2 329967-85-3, Cyclooxygenase 1 338454-52-7, γ-Secretase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT 9000-81-1, Acetylcholinesterase 338455-07-5, α-Secretase
RL: **BSU (Biological study, unclassified); BIOL (Biological study)**
(inhibitors; NSAID and NSAID derivative amyloid Aβ42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Breitner; US 5643960 A 1997 HCAPLUS
(2) Clark; US 5695774 A 1997 HCAPLUS
(3) Garner; US 6160618 A 2000 HCAPLUS
(4) Horrobin; US 5603959 A 1997 HCAPLUS
(5) Lee; US 6184248 B1 2001 HCAPLUS
(6) McGeer; US 5192753 A 1993 HCAPLUS

L43 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:525847** HCAPLUS
DN 135:104271
ED Entered STN: 20 Jul 2001
TI Alzheimer's disease-associated β **-secretase** and amyloid precursor protein substrates and their therapeutic uses
IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy; Parodi, Luis A.; Yan, Riqiang
PA USA
SO PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DT Patent
LA English
ICI C12
CC 7-2 (Enzymes)
Section cross-reference(s): 3, 9, 14

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001050829	A2	20010719	WO 2001-IB799	20010509 <--
	WO 2001050829	A3	20031204		
	W: US				
	US 6699671	B1	20040302	US 1999-416901	19991013 <--
	US 2005080232	A1	20050414	US 2003-477076	20010509 <--
PRAI	US 1999-416901	A1	19991013 <--		
	US 1998-101594P	P	19980924 <--		
	US 1999-155493P	P	19990923 <--		
	US 1999-404133	B2	19990923 <--		

WO 1999-US20881 A2 19990923 <--
WO 2001-IB799 W 20010509

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001050829	ICI	C12	
WO 2001050829	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2005080232	NCL	530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β -**secretase** and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β-peptide (Aβ) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the Caenorhabditis elegans genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β -**secretase** and γ-secretase generates the N-terminus and C-terminus of the Aβ peptide, resp. Because overprodn. of the Aβ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the . **beta.-secretase** have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide form the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

ST secretase amyloid precursor protein processing Alzheimers disease; sequence secretase cDNA human mouse

IT **Alzheimer's disease**
Anti-Alzheimer's agents
Drug screening
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Molecular cloning
Post-translational processing
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Fusion proteins (chimeric proteins)
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **Amyloid precursor proteins**
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Antisense oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line

(CHO, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(HEK125.3, expressing modified APP for processing; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(Hek 293, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(High 5, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT cDNA sequences
(for β -secretase isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Proteins, specific or class
RL: **ARG (Analytical reagent use)**; **ANST (Analytical study)**; USES (Uses)
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(mammalian, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

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IT Escherichia coli
(recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT **Amyloid**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **MFM (Metabolic formation)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(β-; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT **158736-49-3P, β -Secretase**
RL: **BAC (Biological activity or effector, except adverse)**; **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein moiety reduced) 117910-30-2, Glycoprotein (human clone λAPCP168i4 amyloid A4 precursor protein moiety reduced) 123609-04-1, Glycoprotein (human clone pGBP2 amyloid A4 precursor protein moiety reduced) 262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9 **262413-61-6**, 25: PN: SEQID: 22 unclaimed sequence **262413-63-8 262413-65-0 262413-67-2 262413-69-4 262413-71-8 333371-45-2** 333371-47-4 333371-49-6 333371-51-0
RL: **ARU (Analytical role, unclassified)**; **BPR (Biological**

process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 209209-94-9P, Protein (human gene ASP1) 256364-84-8P, Proteinase Asp2 (Mus musculus precursor) 262412-23-7P 262412-25-9P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 251080-00-9P 251080-04-3P 262412-22-6P 262412-24-8P
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-54-5, DNA (human clone 9-110 amyloid A4 glycoprotein cDNA) 262413-58-1 262413-60-5 262413-62-7 262413-66-1 333371-44-1 350264-48-1 350264-49-2 350264-50-5 350264-51-6 350264-52-7 350264-53-8 350264-54-9 350264-55-0 350264-56-1 350264-57-2 350264-58-3 350264-59-4
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 142749-59-5 186142-28-9 252256-37-4 348636-36-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthetic peptide substrate site; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 118427-80-8 164984-29-6 262364-47-6 262364-48-7 262413-81-0 302566-59-2 333322-60-4 333371-30-5 333371-31-6 333371-32-7 333371-33-8 333371-34-9 333371-35-0 333371-37-2 333371-38-3 333371-39-4 333371-40-7 333371-41-8 333371-42-9 333371-43-0 350241-65-5 350241-67-7 350241-69-9 350241-71-3
RL: PRP (Properties)
(unclaimed sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:507467 HCAPLUS
DN 135:104269
ED Entered STN: 13 Jul 2001
TI Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses
IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy; Parodi, Luis A.; Yan, Riqiang
PA USA
SO PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DT Patent
LA English

ICI C12
CC 7-2 (Enzymes)
Section cross-reference(s): 3, 9, 14
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2001049098	A2	20010712	WO 2001-IB798	20010509	<--
	WO 2001049098	A3	20031120			
	W: US					
	US 6699671	B1	20040302	US 1999-416901	19991013	<--
	US 2004234976	A1	20041125	US 2003-476935	20031106	<--
PRAI	US 1999-416901	A1	19991013	<--		
	US 1998-101594P	P	19980924	<--		
	US 1999-155493P	P	19990923	<--		
	US 1999-404133	B2	19990923	<--		
	WO 1999-US20881	A2	19990923	<--		
	WO 2001-IB798	W	20010509			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001049098	ICI	C12	
WO 2001049098	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2004234976	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β - **secretase** and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β-peptide (Aβ) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the Caenorhabditis elegans genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β -**secretase** and γ-secretase generates the N-terminus and C-terminus of the Aβ peptide, resp. Because overprodn. of the Aβ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the . **beta.-secretase** have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide form the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

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(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Antisense oligonucleotides
RL: **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

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(CHO, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(HEK125.3, expressing modified APP for processing; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

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(High 5, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT cDNA sequences
(for β -**secretase** isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

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(of β -**secretase** isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Escherichia coli
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IT **Amyloid**
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RL: **BAC (Biological activity or effector, except adverse)**; **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties);

THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

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262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9
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262413-67-2 262413-69-4 262413-71-8
333371-45-2 333371-47-4 333371-49-6 333371-51-0
RL: ARU (Analytical role, unclassified); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

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350264-58-3 350264-59-4
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(nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

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302566-59-2 333322-60-4 333371-30-5 333371-31-6 333371-32-7
333371-33-8 333371-34-9 333371-35-0 333371-37-2 333371-38-3
333371-39-4 333371-40-7 333371-41-8 333371-42-9 333371-43-0
350241-65-5 350241-67-7 350241-69-9 350241-71-3
RL: PRP (Properties)
(unclaimed sequence; alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:507466** HCAPLUS
DN 135:104268
ED Entered STN: 13 Jul 2001
TI Alzheimer's disease-associated β **-secretase** and amyloid precursor protein substrates and their therapeutic uses
IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy; Parodi, Luis A.; Yan, Riqiang
PA USA
SO PCT Int. Appl., 185 pp.
CODEN: PIXXD2
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CC 7-2 (Enzymes)
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FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2001049097	A2	20010712	WO 2001-IB797	20010509	<--
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	W: US					
	US 6699671	B1	20040302	US 1999-416901	19991013	<--
	US 2003077226	A1	20030424	US 2001-869414	20010627	
	US 6790610	B2	20040914			
PRAI	US 1999-416901	A1	19991013	<--		
	US 1998-101594P	P	19980924	<--		
	US 1999-155493P	P	19990923	<--		
	US 1999-404133	B2	19990923	<--		
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	WO 2001-IB797	W	20010509			

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WO 2001049097	ICI	C12	
WO 2001049097	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2003077226	NCL	424/009.600	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β - **secretase** and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β-peptide (Aβ) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the Caenorhabditis elegans genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β **-secretase** and γ-secretase generates the N-terminus and C-terminus of the Aβ peptide, resp. Because overprodn. of the Aβ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the . **beta.-secretase** have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide form the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

ST secretase amyloid precursor protein processing Alzheimers disease; sequence secretase cDNA human mouse

IT **Alzheimer's disease**
Anti-Alzheimer's agents
Drug screening
Gene therapy
Molecular cloning
Post-translational processing
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Fusion proteins (chimeric proteins)
RL: **ARU (Analytical role, unclassified)**; **BPN (Biosynthetic preparation)**; **THU (Therapeutic use)**; **ANST (Analytical study)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **Amyloid precursor proteins**
RL: **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Antisense oligonucleotides
RL: **THU (Therapeutic use)**; **BIOL (Biological study)**; USES (Uses)
(Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(CHO, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(HEK125.3, expressing modified APP for processing; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(Hek 293, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(High 5, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT cDNA sequences
(for β -**secretase** isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Proteins, specific or class
RL: **ARG (Analytical reagent use)**; **ANST (Analytical study)**; USES (Uses)
(green fluorescent, reporter proteins in marker vectors; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell
(mammalian, recombinant host; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Protein sequences
(of β -**secretase** isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -**secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT Escherichia coli

(recombinant host; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **Amyloid**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **MFM (Metabolic formation)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(β-; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **158736-49-3P**, β **-Secretase**
RL: **BAC (Biological activity or effector, except adverse)**; **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated β **-secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein moiety reduced) 117910-30-2, Glycoprotein (human clone λAPCP168i4 amyloid A4 precursor protein moiety reduced) 123609-04-1, Glycoprotein (human clone pGBP2 amyloid A4 precursor protein moiety reduced) 262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9 **262413-61-6**, 25: PN: SEQID: 22 unclaimed sequence **262413-63-8 262413-65-0 262413-67-2 262413-69-4 262413-71-8 333371-45-2** 333371-47-4 333371-49-6 333371-51-0
RL: **ARU (Analytical role, unclassified)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BUU (Biological use, unclassified)**; PRP (Properties); **ANST (Analytical study)**; **BIOL (Biological study)**; PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **209209-94-9P**, Protein (human gene ASP1) **256364-84-8P**, Proteinase Asp2 (Mus musculus precursor) **262412-23-7P 262412-25-9P**
RL: **BAC (Biological activity or effector, except adverse)**; **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT **251080-00-9P 251080-04-3P 262412-22-6P 262412-24-8P**
RL: **BPN (Biosynthetic preparation)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-54-5, DNA (human clone 9-110 amyloid A4 glycoprotein cDNA) 262413-58-1 **262413-60-5 262413-62-7 262413-66-1 333371-44-1** 350264-48-1 350264-49-2 350264-50-5 350264-51-6 **350264-52-7 350264-53-8 350264-54-9 350264-55-0** 350264-56-1 350264-57-2 350264-58-3 350264-59-4
RL: **BUU (Biological use, unclassified)**; PRP (Properties); **BIOL (Biological study)**; USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β - **secretase** and amyloid precursor protein substrates and their

therapeutic uses)
IT 142749-59-5 186142-28-9 252256-37-4 348636-36-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthetic peptide substrate site; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
IT 262413-81-0 333371-30-5 333371-31-6 333371-32-7 333371-33-8
333371-34-9 333371-35-0 333371-37-2 333371-38-3
RL: PRP (Properties)
(unclaimed nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
IT 118427-80-8 164984-29-6 262364-47-6 262364-48-7 302566-59-2
333322-60-4 333371-39-4 333371-40-7 333371-41-8 333371-42-9
333371-43-0 350241-65-5 350241-67-7 350241-69-9 350241-71-3
RL: PRP (Properties)
(unclaimed sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:513905 HCAPLUS
DN 133:133772
ED Entered STN: 28 Jul 2000
TI Rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening
IN Bamdad, Cynthia Carol; Bamdad, R. Shoshana
PA Minerva Biotechnologies Corporation, USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-68
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1, 15, 17
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000043791	A2	20000727	WO 2000-US1997	20000125 <--
	WO 2000043791	A3	20010726		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2361013	AA	20000727	CA 2000-2361013	20000125 <--
	EP 1169646	A2	20020109	EP 2000-913266	20000125 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002540383	T2	20021126	JP 2000-595161	20000125 <--
	US 2005112607	A1	20050526	US 2004-823097	20040413 <--
PRAI	US 1999-117126P	P	19990125 <--		
	US 1999-132288P	P	19990503 <--		
	US 1999-155937P	P	19990924 <--		
	US 1999-116975P	P	19990123 <--		
	US 1999-132289P	P	19990503 <--		
	US 1999-133148P	P	19990507 <--		
	US 1999-133772P	P	19990512 <--		
	WO 2000-US1504	A2	20000121 <--		
	WO 2000-US1997	W	20000125 <--		
	US 2000-602689	B2	20000623 <--		

US 2000-602778 B2 20000623 <--
US 2000-631818 B2 20000803 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000043791	ICM	G01N033-68
WO 2000043791	ECLA	G01N033/68V2 <--
US 2005112607	NCL	435/006.000
	ECLA	C12Q001/00B; C12Q001/00B4; G01N033/543D; G01N033/543K2B; G01N033/543M; G01N033/58H; G01N033/68V2 <--

AB Methods, assays, and components are described in which biol. samples can be rapidly and sensitively analyzed for the presence of species associated with neurodegenerative disease. Techniques and components are provided for diagnosis of disease, as well as for screening of candidate drugs for treatment of neurodegenerative disease. The techniques are simple, extremely sensitive, and utilize readily-available components. Binding species, capable of binding a neurodegenerative disease aggregate-forming or fibril-forming species, are fastened to surfaces of electrodes and surfaces of particles, or provided free in solution, to bind fibril-forming species and/or be involved in aggregation.

ST aberrant protein fibril aggregation colloid; drug screening neurodegenerative disease kit

IT Brain, disease
Prion diseases
(Creutzfeldt-Jakob; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
(PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
RL: **ANT (Analyte); ANST (Analytical study)**
(PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Voltammetry
(a.c.; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(bovine spongiform encephalopathy; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nervous system
(degeneration; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Self-assembled monolayers
(electroactive; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Carboxyl group
(ionized; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Aggregation
Alzheimer's disease
Blood analysis
Cerebrospinal fluid
Colloids
Diagnosis
Drug screening
Feed
Fibril
Immobilization, biochemical
Magnetic particles

Microtiter plates
Molecular association
Molecular recognition
Parkinson's disease
Test kits
Transplant and Transplantation
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies
RL: **BSU (Biological study, unclassified)**; PEP (Physical, engineering or chemical process); PRP (Properties); **BIOL (Biological study)**; PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Antibodies
DNA
Metallocenes
Nucleic acids
Oligonucleotides
Peptides, properties
Proteins, general, properties
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Brain, disease
(spongiform encephalopathy, transmissible; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Sensors
(surface plasmon resonance chip; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Transferrins
RL: **BSU (Biological study, unclassified)**; PEP (Physical, engineering or chemical process); PRP (Properties); **BIOL (Biological study)**; PROC (Process)
(τ-transferrins; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT **Amyloid**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PROC (Process)
(β-, C-terminal fragment; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT **Amyloid**
RL: **BSU (Biological study, unclassified)**; PEP (Physical, engineering or chemical process); PRP (Properties); **BIOL (Biological study)**; PROC (Process)
(β-; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 58-85-5, Biotin 70-18-8, Glutathione, properties 102-54-5, Ferrocene 573-58-0, Congo Red 2390-54-7, Thioflavin-T 6066-82-6, Succinimide, N-hydroxy 7440-57-5, Gold, properties 9001-78-9, Phosphatase, alkaline 9013-20-1, Streptavidin **158736-49-3**, Secretase
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 139-13-9, Nitrilotriacetic acid 10487-90-8 64691-70-9
RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); PROC (Process); RACT (Reactant or reagent)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT 167396-02-3 286411-43-6 286411-44-7 286411-46-9 286411-47-0

286411-48-1
RL: PRP (Properties)
(unclaimed sequence; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

L43 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:493661 HCAPLUS
DN 133:117175
ED Entered STN: 21 Jul 2000
TI Methods and compositions for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP)
IN Seiffert, Dietmar A.; Mitchell, Thomas J.
PA Dupont Pharmaceuticals Company, USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N
CC 9-10 (Biochemical Methods)
Section cross-reference(s): 1, 3, 6
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2000042166	A2	20000720	WO 2000-US872	20000113	<--
	W: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	US 6518011	B1	20030211	US 2000-481980	20000112	<--
	AU 2000034711	A1	20000801	AU 2000-34711	20000113	<--
	US 2003091983	A1	20030515	US 2002-326049	20021220	<--
PRAI	US 1999-115749P	P	19990113	<--		
	US 2000-481980	A3	20000112	<--		
	WO 2000-US872	W	20000113	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2000042166	ICM	C12N	
WO 2000042166	ECLA	C07K014/47A3; G01N033/68V2	<--
US 6518011	NCL	435/004.000; 435/007.100; 435/007.210; 435/069.100; 435/070.100; 435/320.100; 435/325.000; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; G01N033/68V2	<--
US 2003091983	NCL	435/004.000	
	ECLA	C07K014/47A3; G01N033/68V2	<--

AB The present invention is directed generally to methods and composition for monitoring the processing of epitope-tagged β -APP . More specifically, the present invention relates to the use of such methods and composition for monitoring responses of cells expressing such epitope-tagged β -APP or fragments thereof or cell free systems containing the epitope-tagged polypeptides to therapy of diseases associated with an altered metabolism of the β -APP, and for screening and evaluation of potential drugs for the treatment of these disorders, including Alzheimer's disease (AD). Site-directed mutagenesis was used to incorporate the cDNA sequence for either the myc or HA 11 epitope tag within the A-β fragment of the β -APP 695 isoform. After HEK 293 cells were transfected with the construct, the cell lysates were analyzed by immunoblotting.
ST cellular processing epitope tagged beta amyloid precursor protein; drug screening epitope tagged beta amyloid precursor protein
IT Animal cell line
(293; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT **Amyloid precursor proteins**
RL: **ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);** PREP (Preparation); PROC (Process); USES (Uses)
(APP695, with myc or HA 11 epitope tag in A-β part; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Antibodies
RL: **ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);** PROC (Process); USES (Uses)
(as binding substances binding to epitope tag or other epitope; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Biopolymers
RL: **BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study);** USES (Uses)
(as test compds.; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Gene, animal
RL: **ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);** PREP (Preparation); PROC (Process); USES (Uses)
(c-myc, as epitope tag; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT cDNA
RL: **BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study);** PREP (Preparation); PROC (Process)
(encoding epitope-tagged β-amyloid precursor protein; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Immunoassay
(enzyme-linked immunosorbent assay; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Hemagglutinins
RL: **ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);** PREP (Preparation); PROC (Process); USES (Uses)
(epitope HA 11 of, of influenza, as epitope tag; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Protein degradation
(epitope tag as target for; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Fluids
(epitope-tagged A-β peptides detection in; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Peptides, analysis
RL: **ANT (Analyte); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified);** PUR (Purification or recovery); **ANST (Analytical study); BIOL (Biological study);** PREP (Preparation); PROC

(Process)
(epitope-tagged A-β, detection of; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT **Amyloid precursor proteins**
RL: **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process)
(epitope-tagged; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Animal cell line
(expressing cDNA construct; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Animal tissue
(exts.; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Mutation
(forms of β -APP, epitope tag in relation to; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Immunoassay
(immunoblotting; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Ascitic fluid
Blood
Blood analysis
Cell
Cerebrospinal fluid
Culture media
Drug screening
Epitopes
Molecular cloning
Protein sequences
Urine
Urine analysis
(methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Antibodies
RL: **ARG (Analytical reagent use)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **ANST (Analytical study)**; **BIOL (Biological study)**; PROC (Process); USES (Uses)
(monoclonal, as binding substances binding to epitope tag or other epitope; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT **Anti-Alzheimer's agents**
(screening for and evaluation of; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Molecules
(small, as test compds.; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT Mutation
(splice site, forms of β -APP, epitope tag in relation to; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -APP))

IT 284025-86-1P

RL: **ARU (Analytical role, unclassified)**; PRP (Properties); SPN (Synthetic preparation); **ANST (Analytical study)**; PREP (Preparation)
(as synthetic HA 11 A-β peptide; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT 88191-84-8, MDL 28170
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(as γ-secretase inhibitor, transformed HEK 293 cells response to; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT **158736-49-3**, β -**Secretase**
RL: **ARU (Analytical role, unclassified)**; **THU (Therapeutic use)**; **ANST (Analytical study)**; **BIOL (Biological study)**; USES (Uses)
(binding substance to neoepitope generated by; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT 20350-15-6, Brefeldin A
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(transformed HEK 293 cells response to; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT 284507-22-8, 3: PN: WO0042166 PAGE: 22 unclaimed DNA 284507-23-9, 4: PN: WO0042166 PAGE: 22 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT 134500-80-4 284507-21-7
RL: PRP (Properties)
(unclaimed protein sequence; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

IT 92000-76-5 205437-69-0 284494-16-2
RL: PRP (Properties)
(unclaimed sequence; methods and compns. for monitoring cellular processing of epitope-tagged β-amyloid precursor protein (β -**APP**))

L43 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2000:53695** HCAPLUS
DN 132:102848
ED Entered STN: 23 Jan 2000
TI Interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease
IN Nandabalan, Krishnan; Yang, Meijia; Schulz, Vincent Peter
PA Curagen Corporation, USA
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-00
CC 1-11 (Pharmacology)
Section cross-reference(s): 3, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002911	A2	20000120	WO 1999-US15592	19990708 <--
	WO 2000002911	A3	20010118		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2332625	AA	20000120	CA 1999-2332625	19990708	<--
AU 9948693	A1	20000201	AU 1999-48693	19990708	<--
EP 1095154	A2	20010502	EP 1999-932376	19990708	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002521004	T2	20020716	JP 2000-559140	19990708	<--
PRAI US 1998-113348	A2	19980710	<--		
WO 1999-US15592	W	19990708	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2000002911	ICM	C07K014-00	
WO 2000002911	ECLA	C07K014/47A3; C07K014/81B1A; C12N009/64F2C21	<--

AB The present invention discloses an interaction between β -**APP** and HsLON and the formation of a β -**APP** :HsLON complex, or of the derivs., fragments, analogs and homologs thereof, that were identified using a modified, improved yeast two hybrid assay system. Methodologies of screening these aforementioned complexes for efficacy in treating and/or preventing various diseases and disorders, particularly neurodegenerative disease, cardiomyopathy, diabetes, hearing loss, male infertility, mitochondrial DNA mutation associated disorders and the like, are also disclosed herein.

ST Alzheimer beta amyloid precursor Lon protease HsLON sequence

IT Proteins, specific or class
RL: **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(HsLON (human Lon-protease-like protein); interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Gene, animal
RL: **BPN (Biosynthetic preparation)**; PRP (Properties); **BIOL (Biological study)**; PREP (Preparation)
(HsLON; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Diagnosis
(agents; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Heart, disease
(cardiomyopathy; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Drug delivery systems
(carriers; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Nervous system
(degeneration; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Mutation
(in mitochondrial DNA; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT **Alzheimer's disease**

Antidiabetic agents
Diabetes mellitus
Diagnosis
Drug screening
Fluorescent indicators
Genetic vectors
Molecular cloning
Protein sequences
cDNA sequences
(interaction of human beta amyloid precursor protein (β - **APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Fusion proteins (chimeric proteins)
RL: **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(interaction of human beta amyloid precursor protein (β - **APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT **Amyloid precursor proteins**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; PROC (Process)
(interaction of human beta amyloid precursor protein (β - **APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Primers (nucleic acid)
Probes (nucleic acid)
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PROC (Process); USES (Uses)
(interaction of human beta amyloid precursor protein (β - **APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Antisense oligonucleotides
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; PROC (Process); USES (Uses)
(interaction of human beta amyloid precursor protein (β - **APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Hearing
(loss; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Fertility
(male, disorder; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Mitochondrial DNA
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; PROC (Process)
(mutation in; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Promoter (genetic element)
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(of gene HsLON; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Mutagenesis
(site-directed; interaction of human beta amyloid precursor protein (β -**APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT RNA
RL: **BPN (Biosynthetic preparation)**; PRP (Properties); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(β **-APP-** or HsLON-encoding; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Antibodies
RL: **BPN (Biosynthetic preparation)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); PROC (Process); USES (Uses)
(β **-APP-**HsLON complex-specific; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Gene, animal
RL: **BPN (Biosynthetic preparation)**; PRP (Properties); **BIOL (Biological study)**; PREP (Preparation)
(β **-APP**; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein moiety reduced) 155078-43-6
RL: **BOC (Biological occurrence)**; **BPR (Biological process)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; OCCU (Occurrence); PROC (Process)
(amino acid sequence; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 151002-40-3, GenBank A02759 151579-59-8, GenBank X74215
RL: **BOC (Biological occurrence)**; **BSU (Biological study, unclassified)**; PRP (Properties); **BIOL (Biological study)**; OCCU (Occurrence)
(nucleotide sequence; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 255815-97-5, 1: PN: WO0002911 SEQID: 5 unclaimed DNA 255815-98-6, 2: PN: WO0002911 SEQID: 6 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; interaction of human beta amyloid precursor protein (β **-APP**) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

L43 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1999:795957** HCAPLUS
DN 132:32677
ED Entered STN: 17 Dec 1999
TI β **-secretases** acting on wild-type forms of amyloid precursor protein
IN Rholam, Mohamed; Munoz-Gimenez, Noeli; Moutaouakil, Mohamed; Cohen, Paul; Bertrand, Philippe
PA Rhone-Poulenc Rorer S.A., Fr.; Universite Pierre et Marie Curie Paris VI
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM C12N015-12
ICS C12N015-57; C12N009-64; C07K016-40; C12Q001-37; A61K039-395; A61K038-48; A61K031-70
CC 7-2 (Enzymes)
Section cross-reference(s): 1, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9964587	A1	19991216	WO 1999-FR1326	19990604	<--
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
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	CA 2330242	AA	19991216	CA 1999-2330242	19990604	<--
	AU 9940455	A1	19991230	AU 1999-40455	19990604	<--
	EP 1084240	A1	20010321	EP 1999-923674	19990604	<--
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	JP 2002517239	T2	20020618	JP 2000-553577	19990604	<--
	ZA 2000007118	A	20020201	ZA 2000-7118	20001201	<--
PRAI	FR 1998-7068	A	19980605	<--		
	US 1999-122599P	P	19990331	<--		
	WO 1999-FR1326	W	19990604	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9964587	ICM	C12N015-12	
	ICS	C12N015-57; C12N009-64; C07K016-40; C12Q001-37; A61K039-395; A61K038-48; A61K031-70	
WO 9964587	ECLA	C12N009/64F	<--
FR 2779444	ECLA	C12N009/64F	<--

AB β -**Secretases** that cleave the natural β-amyloid peptide precursor (APP) are identified and characterized. The enzyme may be of use in the treatment of Alzheimer's disease (no data) or in screening for effectors of precursor processing. The enzyme cleaves the protein between methionine-596 and aspartic acid-597 of the wild-type amyloid precursor but not the asparagine-595-leucine-596 double mutant. The enzyme is found in cells not affected by Alzheimer's disease, it has a mol. weight of 70,000 and a pI of .apprx.6.0. The enzyme is a chymotrypsin-like serine proteinase. The enzyme was identified in THP-1 cells that were identified as producing properly cleaved amyloid precursor. Purification was monitored by cleavage of an assay substrate and checking for the correct cleavage product with a monoclonal antibody. Anal. of substrate specificity using a number of analogs of the cleavage site confirmed the activity and specificity of the enzyme.

ST secretase beta wild type amyloid precursor protein cleavage; Alzheimer disease **beta secretase** regulation amyloid processing

IT Animal cell line
(THP-1, β -**secretase** of; β -**secretases** acting on wild-type forms of amyloid precursor protein)

IT **Alzheimer's disease**
(amyloid precursor processing and treatment of; β -**secretases** acting on wild-type forms of amyloid precursor protein)

IT Nervous system
(central, manufacture of β -**secretase** in cells of; β -**secretases** acting on wild-type forms of amyloid precursor protein)

IT Nervous system
(degeneration, amyloid precursor processing and treatment of; β -**secretases** acting on wild-type forms of amyloid precursor protein)

IT **Drug screening**
(for inhibitors of β -**secretase**; β -**secretases** acting on wild-type forms of amyloid precursor protein)

IT Nicotinic receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in secretion and delivery of β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Signal peptides
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in secretion and delivery of β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Immune system
(manufacture of β -secretase in cells of; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Nervous system
(peripheral, manufacture of β -secretase in cells of; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signal peptides of κ-chain of, in secretion and delivery of β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Antibodies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)
IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β -secretases acting on wild-type forms of amyloid precursor protein)
IT 118427-80-8 186142-28-9 252256-37-4 252256-38-5
252256-39-6 252256-40-9 252256-41-0 252256-42-1 252256-43-2
252256-44-3 252256-45-4 252256-46-5 252256-47-6 252256-48-7
252256-49-8 252333-20-3 252333-21-4
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(cleavage by β -secretase of; β -secretases acting on wild-type forms of amyloid precursor protein)
IT 158736-49-3P, β -Secretase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process)
(β -secretases acting on wild-type forms of amyloid precursor protein)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Athena Neurosciences Inc; WO 9207068 A 1992 HCAPLUS
(2) Athena Neurosciences Inc; WO 9640885 A 1996 HCAPLUS
(3) Brown, A; JOURNAL OF NEUROCHEMISTRY 1996, V66(6), P2436 HCAPLUS
(4) Cephalon Inc; WO 9113904 A 1991 HCAPLUS
(5) Evin, G; AMYLOID 1994, V1(4), P263 HCAPLUS
(6) Lilly Co Eli; EP 0576152 A 1993 HCAPLUS
(7) Miles Inc; EP 0569777 A 1993 HCAPLUS
(8) Nelson, R; JOURNAL OF BIOLOGICAL CHEMISTRY 1990, V265(7), P3836 HCAPLUS
(9) Univ Boston; WO 9203542 A 1992 HCAPLUS

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